IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

EDWARDS LIFESCIENCES AG and EDWARD LIFESCIENCES, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 08-091-GMS
COREVALVE, INC. and MEDTRONIC COREVALVE, LLC,	)	
Defendants.	)	

DECLARATION OF JEFFREY J. POPMA, M.D.

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Dated: June 24, 2013

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EDWARDS LIFESCIENCES AG and EDWARDS LIFESCIENCES, LLC, Plaintiffs, v. COREVALVE, INC. and MEDTRONIC COREVALVE, LLC, Defendants. AND RELATED COUNTERCLAIMS.	Case No. C.A. No. 08-091 (GMS)

DECLARATION OF JEFFREY J. POPMA, M.D.

I. INTRODUCTION

I, Jeffrey J. Popma, M.D., declare under penalty of perjury that:

1. I am the Director, Interventional Cardiology Clinical Services at the Beth Israel Deaconess Medical Center, Boston, MA, and a Professor of Medicine at Harvard Medical School in Boston.

2. I am writing this Declaration to outline the significant, life-threatening detriment to patients in the United States if the Medtronic CoreValve Transcatheter Heart Valve (THV) cannot be commercialized and sold at the time of FDA approval.

II. PROFESSIONAL BACKGROUND

3. I received my M.D. with highest honors in 1981 from Indiana University School of Medicine, Indianapolis, IN. I completed a Flexible Internship in Emergency Medicine from 1981-1982 at the University of San Francisco-Valley Medical Center in Fresno, California. From 1982 through 1989, I was an intern, resident, and Chief Resident in Internal Medicine, and then Fellow in Cardiology, at University of Texas-Southwestern Medical Center, Dallas, Texas.

4. From 1989 to 1990, I was a Fellow in Interventional Cardiology at the University of Michigan, Ann Arbor, Michigan. I was also appointed Associate Professor of Medicine, specializing in interventional cardiology.

5. Since 1999, I have been on the faculty of Harvard Medical School, first as Instructor, then as Associate Professor until 2007, then as Lecturer from 2008-2009, and again as Associate Professor from 2009-2012. I became a Professor of Medicine at Harvard Medical School in May, 2012 and currently hold this position.

6. I have been an interventional cardiologist since 1991 and have been a practicing Interventional Cardiologist from 1991 until the present time.

7. I was the Director of the Washington Hospital Center Angiographic Core Laboratory from 1991-1998 which specialized in the measurement of coronary arteries and assessment of coronary flow.

8. I was Director of Interventional Cardiology from 1998 to 2007 and Director of the Angiographic Core Laboratory from 1998-2009 at Brigham and Women's Hospital, Boston, Massachusetts.

9. From 2007-2009, I was Director of the Cardiac Catheterization Laboratory and Director of Invasive Cardiovascular Services at Caritas Christi Health Care System, Boston, Massachusetts.

10. Since 2009, I have been Director of Interventional Cardiology Clinical Services, and Director of the Angiographic Core Laboratory at Beth Israel Deaconess Medical Center, Boston, Massachusetts.

11. In my years as an interventional cardiologist, I have performed more than 5,000 cardiac procedures.

12. I have been a principal investigator for a number of angiographic studies of medical devices used in PCI, including new stents and coronary guidewires.

13. I have lectured widely and as an invited speaker at numerous academic meetings, academic institutions, and hospitals.

14. I have published over 350 peer-reviewed articles regarding interventional cardiology, written 10 book chapters, and edited 5 interventional-cardiology textbooks.

15. I am the National Co-Principal Investigator of the Medtronic CoreValve US Pivotal Trials for patients who are at Extreme or High-Risk for surgical aortic valve replacement.

16. I have attended the Edwards SAPIEN Training sessions for commercial use and observed SAPIEN cases in our institution. I have referred patients in my aortic valve practice for SAPIEN TAVR.

III. COMPENSATION

1. I am not being compensated for this Declaration.

IV. CLINICALLY IMPORTANT STRUCTURAL, DEPLOYMENT AND DELIVERY DIFFERENCES BETWEEN THE SAPIEN THV AND THE COREVALVE THV

1. The Edwards SAPIEN THV with the Retroflex Delivery System is a balloon-expandable THV that is commercially available in the United States in 23 mm and 26 mm sizes. The Edwards Instructions For Use (IFU) for this device **(Appendix A)** state that patients with annular diameters smaller than 18 mm and larger than 25 mm cannot be treated with the Sapien THV.

2. In my experience, approximately 20-30% of patients with aortic stenosis have an aortic annular diameter larger than 25 mm. Approximately 18,000 TAVR procedures will be performed in the United States in 2014 **(Appendix B)**. This would mean that approximately 3,600-5,400 patients with larger than 25 mm aortic valve diameters could not be treated if the CoreValve THV were not allowed to be sold in the United States, and these patients would be at substantial (up to 50%) risk for death and severe morbidity over the ensuing year.

3. Deployment of the balloon-expandable SAPIEN THV in patients with a severely calcified annulus may result in annular rupture **(Appendix I)**, which may be fatal **(Appendix C)** (Blanke, et. al., Circ Cardiovasc Interv 2012). In contrast, the CoreValve THV is a self-expanding frame that does not cause annular rupture after deployment. As a result, patients with severely calcified valves would be placed at

substantial risk of death if the CoreValve device were precluded from sales in the United States.

4. According to the SAPIEN THV IFU, the SAPIEN THV also must be used with caution in patients with bulky calcified aortic valve leaflets in close proximity to coronary ostia due to the risk of coronary occlusion. According to recent presentations, the SAPIEN THV also presents risks of coronary occlusion where the coronary arteries are less than 8 mm above the aortic annulus **(Appendix D)** (Ribeiro et al JACC: Cardiovascular Interventional Cardiology). Unlike the SAPIEN THV, the CoreValve THV has a self-expanding Nitinol frame, which permits adequate coronary artery perfusion after deployment.

5. The CoreValve THV has a "supra-annular" valve location, in contrast to the SAPIEN THV where the valve is located in the aortic annulus. There are two reasons why this is important. First, in the setting of a prominent septal bulge within the left ventricular outflow tract, the SAPIEN balloon expandable THV can be expelled from the aortic annulus into the aorta or dislodged into the left ventricle, which are dangerous and potentially lethal conditions. The supra-annular location of the CoreValve THV and the self-expanding delivery results in a much lower risk of dislodgement in patients with a prominent septal bulge. Second, the location of the THV is important in cases in which an eccentric annulus cannot be reshaped with the balloon-expandable SAPIEN THV **(Appendix E)** (Allam, et. al., J Interven Cardiol, 2011). In this setting, an eccentric SAPIEN THV placement will preclude aortic valve coaptation (sealing of the valve leaflets) and result in residual aortic regurgitation (backflow of blood into the ventricle), which has a higher risk of death.

6. Deployment of the SAPIEN balloon-expandable THV also requires rapid ventricular pacing (up to 200 beats per minute). In patients with poor left ventricular ejection fraction resulting in heart failure, rapid pacing can place the patient at risk for arrhythmias **(Appendix I)**. Deployment of the CoreValve THV does not require

rapid ventricular pacing, and places the patient at lower risk for complications during the procedure.

7. In addition to the design issues that differentiate these two devices, there are differences in ease of use during the deployment that are important for physicians. Specifically, there are no options for repositioning of the SAPIEN THV after balloon inflation. In contrast, the CoreValve THV is partially repositionable, allowing the CoreValve THV to be retracted (and removed if needed) to optimize the valve performance.

8. According to the SAPIEN THV IFU, the patient's iliofemoral diameter must be at least 7 mm in order to allow delivery of the SAPIEN THV **(Appendix A)**. Moreover, delivery of the SAPIEN THV may be difficult in patients with severe iliofemoral tortuosity or severe calcification.

9. In my experience, approximately 20% of patients currently treated with the CoreValve THV have an iliofemoral diameter smaller than 7 mm. This means that approximately 3,600 patients per year would not be able to be treated by the current SAPIEN THV if the CoreValve THV were precluded from sales in the United States.

10. The SAPIEN THV IFU states that the SAPIEN THV should be used with caution if there is marked tortuosity and unfolding of the thoracic aorta. In contrast, the more flexible delivery catheter of the CoreValve THV can be used to safely treat many patients with these conditions. Those patients could not be treated if the CoreValve device were not available for sale in the United States.

V. CLINICALLY IMPORTANT STRUCTURAL, DEPLOYMENT AND DELIVERY DIFFERENCES BETWEEN THE SAPIEN XT THV AND THE COREVALVE THV

11. In the event that the SAPIEN XT THV is commercially approved in the United States, according to the SAPIEN XT IFU **(Appendix F)**, patients with an aortic annulus greater than 27 mm cannot be treated with the 29 mm SAPIEN XT THV. In my experience, approximately 10% of aortic stenosis patients have an aortic annular diameter between 27 mm and 29 mm. These patients are eligible for treatment with a 31 mm CoreValve THV. Assuming 18,000 TAVR procedures in 2014, approximately 1,800 patients would be without treatment options if the CoreValve THV were precluded from sales in the United States.

12. In addition, for patients with annular diameter less than 27 mm, all of the concerns described in Paragraph 3-7 and Paragraph 10 would still apply if the CoreValve THV were precluded from sale in the United States.

13. Moderate or severe post-procedural transvalvular aortic regurgitation is an important predictor of death after TAVR. The incidence of one year moderate/severe transvalvular aortic regurgitation was 29.7% with the SAPIEN XT THV compared with 22.4% with the predicate SAPIEN THV, which was higher than the aortic regurgitation rates 30 days after the procedure (24.8% and 21.3%, respectively) **(Appendix G)**.

14. In contrast, moderate or severe aortic regurgitation was 13% at one year after treatment with the CoreValve THV, which was lower than the 15% rate observed at 30 days in the ADVANCE Study reported by Alex Linke at the EuroPCR on May 20, 2013 in Paris **(Appendix H)**.

15. The relatively high rate of aortic regurgitation seen one year after implantation of the SAPIEN XT device, and its worsening over time possibly due to the cobalt chromium

frame, requires further study. The lower rates of aortic regurgitation after CoreValve THV may provide better long-term outcomes, and the inability to sell the CoreValve device in the United States may place patients at risk.

VI. SUMMARY

In summary, there are clinically compelling design differences between the SAPIEN THV and the CoreValve THV that would place patients at risk for complications and death if the CoreValve device were not available for sale in the United States. Based on the currently available SAPIEN devices in the United States, approximately 20-30% of patients would not be eligible for treatment due to annular sizing and iliofemoral diameter if the CoreValve THV were not available for sale. Even if the SAPIEN XT is commercially approved in the United States, approximately 10% of patients would not be eligible for treatment with the SAPIEN XT due to annular sizing, whereas they could be treated with the CoreValve THV. In addition, there are a substantial number of patients who have anatomy findings that place them at higher risk for complications with the SAPIEN THV or the SAPIEN XT THV and may be better served with the CoreValve THV. Thus, precluding the sale of the CoreValve THV would have a substantial adverse impact on the health and life expectancy of patients who could not be treated with the SAPIEN THV or the SAPIEN XT THV. The impact of this for many patients would be fatal.

I declare under penalty of perjury that the foregoing is true and correct. Executed on June 13, 2013, at Vancouver, Canada.

Jeffrey J Popma

JEFFREY J. POPMA, M.D.

APPENDIX A

Edwards SAPIEN
Transcatheter Heart Valve with the RetroFlex 3 Delivery System

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Please verify that you have the latest version of the instructions for use prior to using the device.

Transfemoral Retrograde Approach

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

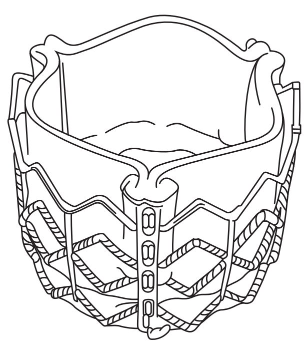
1.0 Device Description

- Edwards SAPIEN Transcatheter Heart Valve – Model 9000TFX (Figure 1)

The Edwards SAPIEN transcatheter heart valve (bioprosthesis) is comprised of a balloon-expandable, radiopaque, stainless steel (316 L) frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermaFix process, packaged, and terminally sterilized in glutaraldehyde.

Figure 1. Edwards SAPIEN Transcatheter Heart Valve

THV01



Bioprosthesis Diameter	Frame Height (Profile)
23 mm	14.3 mm
26 mm	16.1 mm

Edwards Lifesciences, the stylized E logo, Edwards, Edwards SAPIEN, RetroFlex, RetroFlex 3, and ThermaFix are trademarks of Edwards Lifesciences Corporation.

The following table identifies the bioprosthesis size that should be used based on native valve annulus size, as measured by transesophageal echocardiography (TEE).

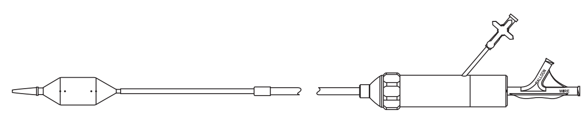
Native Valve Annulus Size (Tissue Annulus Diameter)	Bioprosthesis Diameter
18-22 mm	23 mm
21-25 mm	26 mm

- RetroFlex 3 Delivery System – Model 9120FS23 for 23 mm valve procedure and 9120FS26 for 26 mm valve procedure (Figure 2)

The RetroFlex 3 delivery system includes a rotating wheel within the handle for articulation of flex catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, a balloon for deployment of the bioprosthesis, and radiopaque markers as indicated in Figure 2.

Figure 2. RetroFlex 3 Delivery System

THV112



Black dots indicate position of radiopaque markers.

Nominal Balloon Diameter	RBP
23 mm	7 ATM (709 kPa)
26 mm	7 ATM (709 kPa)

The following table identifies the access vessel diameters that should be used for delivery system access.

Ilio-Femoral Vessel Diameter	Delivery System
≥ 7 mm	23 mm
≥ 8 mm	26 mm

2.0 Indications

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, and RetroFlex 3 Delivery System are indicated for transfemoral delivery in patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

3.0 Contraindications

The bioprosthesis is contraindicated in patients with:

- Non-calcified aortic annulus;
- Congenital unicuspid or congenital bicuspid aortic valve;
- Evidence of intracardiac mass, thrombus or vegetation, active infection or endocarditis.

4.0 Warnings

- The devices are designed, intended, and distributed for single use only. **Do not re-sterilize or reuse the devices.** There are no data to support the sterility, non-pyrogenicity, and functionality of the devices after reprocessing.
- Incorrect sizing of the bioprosthesis may lead to paravalvular leak, migration, embolization and/or annular rupture.
- Accelerated deterioration of the bioprosthesis may occur in patients with an altered calcium metabolism.
- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- Bioprosthesis must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Bioprosthesis leaflets mishandled or damaged during any part of the procedure will require replacement of the bioprosthesis.
- Caution should be exercised in implanting a bioprosthesis in patients with clinically significant coronary artery disease.
- Patients with pre-existing mitral valve devices should be carefully assessed prior to implantation of the bioprosthesis to ensure proper bioprosthesis positioning and deployment.
- Patients presenting with combination AV low flow, low gradient should undergo additional evaluation to establish the degree of aortic stenosis.
- Do not use the bioprosthesis if the tamper evident seal is broken, the storage solution does not completely cover the bioprosthesis, the temperature indicator has been activated, or the bioprosthesis is damaged, or the expiration date has elapsed.
- Do not mishandle the RetroFlex 3 delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.
- The safety of the bioprosthesis implantation has not been established in patients who have:
    - Pre-existing prosthetic heart valve in the aortic position
    - Severe ventricular dysfunction with ejection fraction <20%
    - Hypertrophic cardiomyopathy with or without obstruction (HOCM)

5.0 Precautions

- Long-term durability has not been established for the bioprosthesis. Regular medical follow-up is advised to evaluate bioprosthesis performance.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to Material Safety Data Sheet available from Edwards Lifesciences.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.
- Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.
- Bioprosthetic valve recipients should be maintained on anticoagulant and antiplatelet therapy (e.g. clopidogrel or ticlopidine [75 mg/day]) for 6 months post procedure and aspirin (75-100 mg/day) for life, except when contraindicated, as determined by their physician.

6.0 Potential Adverse Events

- Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization for the transfemoral access procedure, balloon valvuloplasty, and the potential risks of local and/or general anesthesia: abnormal lab values (including electrolyte imbalance); allergic reaction to anesthesia or to contrast media; anemia; angina; arrhythmia; bleeding; cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention; conduction system injury (defect) which may require a permanent pacemaker; death; embolization including air, calcific valve material or thrombus; exercise intolerance or weakness; femoral AV fistula or pseudoaneurysm; fever; heart failure; heart murmur; hematoma; hemorrhage requiring transfusion or intervention; hypertension or hypotension; infection including septicemia and endocarditis; inflammation; myocardial infarction; pain or changes at the access site; paralysis; pericardial effusion or cardiac tamponade; peripheral ischemia or nerve injury; permanent disability; pleural effusion; pulmonary edema; renal insufficiency or renal failure; reoperation; respiratory insufficiency or respiratory failure; restenosis; retroperitoneal bleed; stroke/transient ischemic attack, clusters or neurological deficit; syncope.
- Additional potential risks specifically associated with the use of the bioprosthesis include, but may not be limited to the following: bleeding; cardiac arrest; cardiac failure or low cardiac output; cardiogenic shock; coronary flow obstruction/transvalvular flow disturbance; device degeneration; device embolization; device explant; device migration or malposition requiring intervention; device thrombosis requiring intervention; emergency cardiac surgery; endocarditis; hemolysis; hemorrhage; injury at the site of venous, arterial or ventricular access that may require repair; non-emergent reoperation; nonstructural

dysfunction; paravalvular/or transvalvular leak; structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflets retraction, stent creep, suture line disruption of components of a prosthetic valve, thickening, stenosis, or other); valve regurgitation; valve stenosis; valve deployment in unintended location; valve thrombosis.

All listed risks may include symptoms associated with the above mentioned medical conditions.

7.0 Directions for Use

7.1 Required Equipment

- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.035 inch (0.89 mm) extra-stiff guidewire
- Temporary pacemaker (PM) and pacing lead
- Sterile rinsing basins, physiological saline, heparinized saline, and 15% diluted radiopaque contrast medium
- 20 cc or larger luer-lock syringe
- High-pressure 3-way stopcock
- Edwards SAPIEN Transcatheter Heart Valve
- RetroFlex 3 Delivery System
- 20 mm and/or 23 mm balloon catheter such as: RetroFlex balloon catheter Model 9120BC20 for use prior to 23 mm valve implantation and Model 9120BC23 for use prior to 26 mm valve implantation
- RetroFlex 3 Introducer Sheath Set Model 9120S23 for 23 mm valve procedure and Model 9120S26 for 26 mm valve procedure
- RetroFlex Dilator Kit Model 9100DKS7
- Crimper Model 9100CR23 for 23 mm valve procedure and Model 9100CR26 for 26 mm valve procedure
- Inflation device provided by Edwards Lifesciences for this application

7.2 Bioprosthesis Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Bioprosthesis Rinsing Procedure

The bioprosthesis is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: Bioprosthetic valves from containers found to be damaged, leaking, without adequate sterilant, or missing intact seals must not be used for implantation.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 mL of sterile physiologic saline to thoroughly rinse the glutaraldehyde sterilant from the bioprosthesis.
2	The bioprosthesis is contained in the jar within a holder. Carefully remove the bioprosthesis/holder assembly from the jar without touching the tissue. The holder is tagged with the bioprosthesis' serial identification number. Inspect the bioprosthesis for any signs of damage to the frame or tissue.
3	Rinse the bioprosthesis as follows: Place the bioprosthesis in the first bowl of sterile, physiological saline. Be sure the saline solution completely covers the bioprosthesis and holder. With the bioprosthesis and holder submerged, slowly agitate (to **gently** swirl the bioprosthesis and holder) back and forth for a minimum of 1 minute. Transfer the bioprosthesis and holder to the second rinsing bowl of physiological saline and gently agitate for at least one more minute. Ensure the rinse solution in the first bowl is not used. The bioprosthesis should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: Do not allow the bioprosthesis to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the bioprosthesis. Care must be taken to ensure that the identification tag does not come in contact with the tissue and damage it. No other objects should be placed in the rinse bowls. The bioprosthesis should be kept hydrated throughout the rest of the preparation procedure to prevent the tissue from drying.**

7.2.2 Prepare Transfemoral Procedure Components

Step	Procedure
1	Refer to RetroFlex Dilator Kit, RetroFlex 3 Introducer Sheath Set and Crimper instructions for use on device preparation and handling.
2	Prime and flush the guidewire lumen of the delivery system with heparinized saline.
3	Insert an extra stiff guidewire [0.035 inch (0.89 mm) and $\geq$ 150 cm long] in the guidewire lumen, leaving a 2 to 3 cm segment of the guidewire protruding from the distal tip.
4	Flush the delivery system with heparinized saline through the flush port.

Step	Procedure
5	Place the loader cap onto the delivery system, ensuring that the inside of the loader cap is in the same direction as the tapered tip.
6	Prepare a 20 mL or larger luer-lock syringe with diluted contrast medium (15:85 contrast to heparinized saline) and attach it to a 3-way stopcock on the balloon inflation port.
7	Completely fill the inflation device provided by Edwards and attach to 3-way stopcock. Ensure there are no air bubbles in the balloon. If an air bubble is detected, eliminate it while deflating the balloon. Close the stopcock to the syringe.
8	• Insert the balloon into the balloon gauge located on the crimper. Inflate the balloon and verify its diameter fits the gauge with minimal friction. While gently pulling and pushing the balloon, verify that the balloon moves with some resistance within the gauge. If the balloon does not reach the correct diameter when fully inflated, add or discard some of the inflating solution in the inflation device provided by Edwards until the correct diameter is reached. The inflation device must remain connected to the delivery system throughout the rest of the procedure. **Note:** Correct balloon sizing is critical to successful valve deployment and valve function.
9	Close stopcock to the delivery system and remove any remaining contrast solution in inflation provided by Edwards Lifesciences to syringe. Lock the inflation device.
10	Close the stopcock to the 20 mL syringe and verify the balloon is sized appropriately with the gauge. Remove the syringe. Unlock inflation device and deflate the balloon while creating a three-wing fold configuration, and ensure no fluid is left behind. Lock the inflation device.

7.2.3 Mount and Crimp the Bioprosthesis on the Delivery System

Step	Procedure
1	Remove the bioprosthesis from the holder and gently place the bioprosthesis into the crimper aperture.
2	Gradually crimp the bioprosthesis to a diameter of approximately 12 mm.
3	Remove the bioprosthesis from the crimper and place it on the delivery system with the inflow (fabric cuff end) of the bioprosthesis towards the **distal end** of the balloon catheter. Ensure that the inflow of the bioprosthesis is aligned with the proximal end of the tapered catheter tip.
4	Place the bioprosthesis back in the crimper aperture, and completely crimp until it fits inside the crimp gauge. **CAUTION: The physician must verify correct mounting/orientation of the bioprosthesis prior to its implantation.**
5	Press on the balloon shoulders circumferentially to facilitate insertion into the flex catheter and loader.
6	Pull the proximal end of the balloon into the flex catheter until the proximal edge of the bioprosthesis is flush against the distal end of the flex catheter.
7	Flush the loader with sterile heparinized saline and insert the crimped bioprosthesis inside the loader.
8	Advance the bioprosthesis into the loader until the distal end of the delivery system tip is exposed.
9	Screw the loader cap to the loader and re-flush the flex catheter and close the stopcock to the delivery system. **Note:** Keep bioprosthesis hydrated until ready for implantation.
10	Remove guidewire and flush guidewire lumen.

7.3 Valvuloplasty and Bioprosthesis Delivery

Valvuloplasty and bioprosthesis delivery should be performed under local and/or general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and electrocardiographic imaging capabilities.

Administer heparin to maintain the ACT at ≥ 250 sec.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

Note: Use of the retrograde approach may require a femoral artery cut-down with surgical closure of the puncture site due to the large size of the arteriotomy.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the view.
2	Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.

Step	Procedure
3	Introduce a pacemaker (PM) lead until its distal end is positioned in the right ventricle.
4	Set the stimulation parameters, and test pacing.

7.3.2 Valvuloplasty

Refer to RetroFlex Balloon Catheter Instructions for Use (IFU) for information on device preparation and handling.

Note: Rapid ventricular pacing should be performed when using the RetroFlex balloon catheter for valvuloplasty prior to aortic transcatheter valve implantation.

After placement of the balloon at the intended site, begin rapid ventricular pacing. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.

CAUTION: Prosthetic valve implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.

7.3.3 Bioprosthesis Delivery

Step	Procedure
1	Dilate the femoro-iliac vessel using the RetroFlex dilator kit. Refer to RetroFlex Dilator Kit IFU for information on device preparation and handling.
2	Insert the introducer sheath. Refer to the RetroFlex 3 Introducer Sheath Set IFU for additional information on device preparation and handling.
3	Insert the loader into the sheath.
4	Push the delivery system through the sheath. **CAUTION: The bioprosthesis should not be advanced through the sheath if the sheath tip is not past the aortic bifurcation.**
5	Retract loader to the proximal end of RetroFlex 3 delivery system.
6	The catheter articulates in a direction opposite from the flush port, and the flush port should be pointed away from the physician. Advance the RetroFlex 3 delivery system up the descending aorta; deflect the delivery system by rotating its handle "clockwise".
7	Cross the native aortic valve and position the bioprosthesis within the diseased valve.
8	Maintain the position of the bioprosthesis and retract the flex catheter, leaving the bioprosthesis in position. Verify that the flex catheter is completely off of the balloon before it is inflated and the bioprosthesis is deployed.
9	Position the mid-point of the bioprosthesis at the plane of the hinge points of the native valve leaflets.
10	Verify the correct location of the bioprosthesis with respect to the calcified valve.
11	Begin bioprosthesis deployment: • Unlock the inflation device. • Begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the bioprosthesis by inflating the balloon with the entire volume in the inflation device. When the delivery system has been completely deflated, turn off the pacemaker. • De-articulate the delivery system and remove it from the sheath. **CAUTION: Patient injury could occur if the delivery system is not un-flexed prior to removal.**
12	Remove sheath when the ACT level is appropriate (e.g., reaches < 150 sec). Close puncture site.

8.0 How Supplied

STERILE: The bioprosthesis is sterilized with glutaraldehyde solution. The delivery system is sterilized with ethylene oxide gas.

8.1 Storage

The bioprosthesis must be stored between 10 °C-25 °C (50 °F-77 °F). Each jar is shipped in an enclosure containing a temperature indicator to detect exposure of the bioprosthesis to extreme temperature.

The RetroFlex 3 delivery system should be stored in a cool, dry place.

9.0 MR Safety

MR **MR Conditional**

Non-clinical testing has demonstrated that the Edwards SAPIEN THV (implant) is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3 Tesla.

- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33 Ed. 3.0, of the MR system.

In non-clinical testing and analysis, the implant was determined to produce a temperature rise of less than 1.1 °C above background for a whole body SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5 T cylindrical whole body MR system, assessed using a GE Signa whole body coil and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.2 W/kg and local background SAR at the site of the implant was 5.6 W/kg. The measured rise above background was 0.7 °C for a whole body SAR of 2 W/kg in a 3.0 T cylindrical bore whole body MR system, assessed using a GE Signa HDx whole body active shield MR scanner with software version 14/LX/MR and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.9 W/kg and local background SAR at the site of the implant was 8.4 W/kg.

The image artifact extended as far as 15 mm from the implant for spin echo images and 40 mm for gradient images when scanned in non-clinical testing in a 3.0 T GE Signa HDx MR system. The implant has not been evaluated in MR systems other than 1.5 or 3.0 T.

10.0 Patient Information

A patient implant card is provided in the patient information brochure and should be given to every patient after the procedure prior to discharge. The serial number and model number may be found on the package.

11.0 Recovered Clinical Bioprosthesis

The explanted bioprosthesis should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Disposal of Used Devices

Used devices may be disposed of in the same manner that hospital waste and biohazardous materials are handled. There are no special risks related to the disposal of these devices.

12.0 Clinical Studies (see Ref. 1)

The Placement of Aortic Transcatheter Valves (PARTNER) trial, a prospective, randomized-controlled, multi-center pivotal trial, evaluated the safety and effectiveness of the Edwards SAPIEN™ Transcatheter Heart Valve via transfemoral and transapical delivery to the standard therapy of patients in a stratified population of high-risk and inoperable patients with severe symptomatic aortic stenosis. Patients were stratified into two cohorts based on their risk of operability for standard aortic valve replacement surgery - those who were considered high surgical risk were eligible for Cohort A, while inoperable patients were eligible for Cohort B due to coexisting conditions that resulted in the probability of death or irreversible morbidity exceeding 50%. In Cohort A, patients were evaluated for transfemoral access, and those meeting the criteria were 1:1 randomized to either Transfemoral delivery of the Edwards SAPIEN valve or surgical aortic valve replacement. Patients stratified into Cohort B were also evaluated for vascular access and those meeting the criteria were 1:1 randomized to either Transfemoral delivery of the Edwards SAPIEN valve or best medical management. Patients receiving best medical management were treated with medication and/or balloon valvuloplasty. Patients in Cohort B who did not meet the criteria for vascular access were not eligible for the trial. The following data summarize the 1-year results from Cohort B.

A total of 358 patients with severe aortic stenosis underwent 1:1 randomization at 22 centers (18 in the United States) with baseline characteristics described in Table 1. Severe aortic stenosis was defined as an aortic-valve area of less than 0.8 cm^2, a mean aortic-valve gradient of 40 mmHg or more, or a peak aortic-jet velocity of 4.0 m per second or more. The primary end point was the rate of death from any cause over the duration of the trial. At 1 year, the rate of death from any cause (Kaplan-Meier analysis) was 30.7% with TAVR, as compared with 50.7% with standard therapy (hazard ratio with TAVR, 0.51; 95% confidence interval [CI], 0.39 to 0.68; $P < 0.001$) (Figure 3). The coprimary composite end point was time of death from any cause or the time to the first occurrence of repeat hospitalization. The rate of the composite end point of death from any cause or repeat hospitalization was 43.6% with TAVR as compared with 71.6% with standard therapy (hazard ratio, 0.45; 95% CI, 0.35 to 0.59; $P < 0.001$) (Figure 4). Prespecified secondary end points included the rate of death from cardiovascular causes (Figure 5), NYHA functional class (Figure 6), valve performance (Figure 7, 8), and the distance covered during a 6-minute walk test (Figure 9). Among survivors at 1 year, the rate of cardiac symptoms (New York Heart Association class III or IV) was lower among patients who had undergone TAVR than among those who had received standard therapy (23.9% vs. 60.8%, $P < 0.001$). At 30 days, TAVR, as compared with standard therapy, was associated with a higher incidence of strokes (7.3% vs. 1.7%, $P = 0.02$) and major vascular complications (16.8% vs. 1.1%, $P < 0.001$). Clinical outcomes of TAVR as compared with standard therapy are summarized in Table 2. In the year after TAVR, there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of stenosis or regurgitation on an echocardiogram.

In patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular events.

13.0 References

1. Leon, Martin et al. Transcatheter Aortic Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. *N Engl J Med.* 2010, 1-11. This article (10.1053/NEJMoa1008232) was published on September 22, 2010 at NEJM.org

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 5,411,552; 5,840,081; 5,931,969; 6,168,614; 6,210,957; 6,214,054; 6,547,827; 6,561,970; 6,582,462; 6,893,460; 6,908,481; 7,214,344; 7,510,575; 7,530,253; 7,585,321; 7,618,446; 7,780,723; 7,789,909; and RE40570 and corresponding foreign patents. Additional patents are pending.

Table 1: Baseline Characteristics of the Patients and Echocardiographic Findings*			
	TAVR	Standard Therapy	
Characteristic	(N = 179)	(N = 179)	P Value
Age — yr	83.1 ± 8.6	83.2 ± 8.3	0.95
Male sex — no. (%)	82 (45.8)	84 (46.9)	0.92
STS score†	11.2 ± 5.8	11.9 ± 4.8	0.14
Logistic EuroSCORE‡	26.4 ± 17.2	30.4 ± 19.1	0.04
NYHA class — no. (%):			0.68
II	14 (7.8)	11 (6.1)	
III or IV	165 (92.2)	168 (93.9)	
Coronary artery disease — no. (%)	121 (67.6)	133 (74.3)	0.2
Previous myocardial infarction — no./total no. (%)	33/177 (18.6)	47/179 (26.3)	0.10
Previous intervention — no./total no. (%)			
CABG	58/179 (32.4)	73/179 (40.8)	0.12
PCI	47/179 (26.3)	39/179 (21.8)	0.39
Balloon aortic valvuloplasty	25/154 (16.2)	39/160 (24.4)	0.09
Cerebral vascular disease — no./total no. (%)	48/175 (27.4)	46/171 (26.9)	1.00
Peripheral vascular disease — no./total no. (%)	55/178 (30.9)	45/179 (25.1)	0.24
COPD — no. (%):			
Any	74 (41.3)	94 (52.5)	0.04
Oxygen-dependent	38 (21.2)	46 (25.7)	0.38
Creatinine > 2 mg/dL (177 µmol/liter) — no./total no. (%)	8/179 (4.5)	16/178 (9.0)	0.10
Atrial fibrillation — no./total no. (%)	28/85 (32.9)	39/80 (48.8)	0.04
Permanent pacemaker — no./total no. (%)	35/179 (19.6)	31/179 (17.3)	0.68
Pulmonary hypertension — no./total no. (%)	50/118 (42.4)	53/121 (43.8)	0.9
Frailty — no./total no. (%)§	21/116 (18.1)	33/118 (28.0)	0.09
Extensively calcified aorta — no. (%)	34 (19.0)	20 (11.2)	0.05
Deleterious effects of chest-wall irradiation — no. (%)	16 (8.9)	15 (8.4)	1
Chest-wall deformity — no. (%)	15 (8.4)	9 (5.0)	0.29
Liver disease — no./total no. (%)	6/177 (3.4)	6/178 (3.4)	1
Echocardiographic findings			
Aortic-valve area — cm^2	0.6 ± 0.2	0.6 ± 0.2	0.97
Mean aortic-valve gradient — mmHg	44.5 ± 15.7	43.0 ± 15.3	0.39
Mean LVEF — %	53.9 ± 13.1	51.1 ± 14.3	0.06
Moderate or severe mitral regurgitation — no./total no. (%)¶	38/171 (22.2)	38/165 (23.0)	0.9

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve implantation.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk.

§ Frailty was determined by the surgeons according to prespecified criteria.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Figure 3

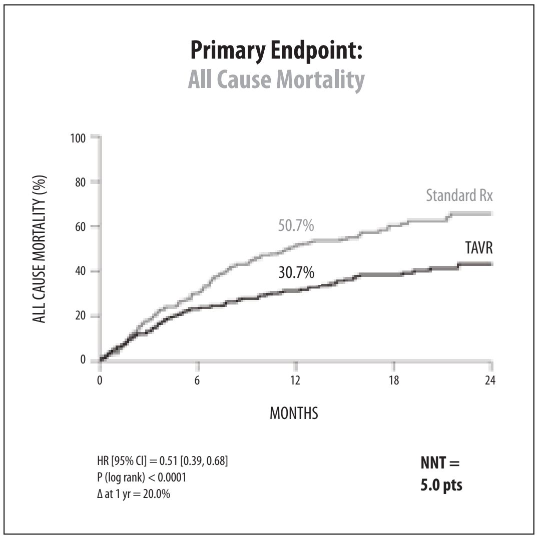


Figure 5

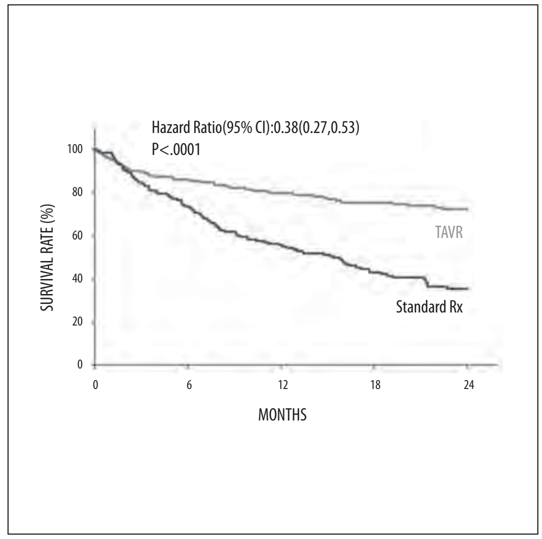


Figure 4

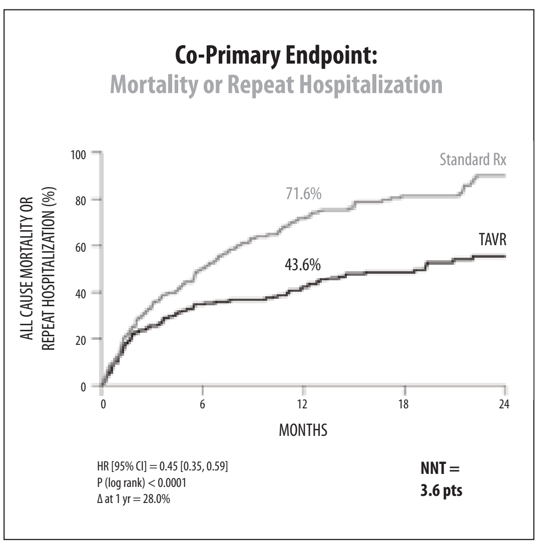


Figure 6

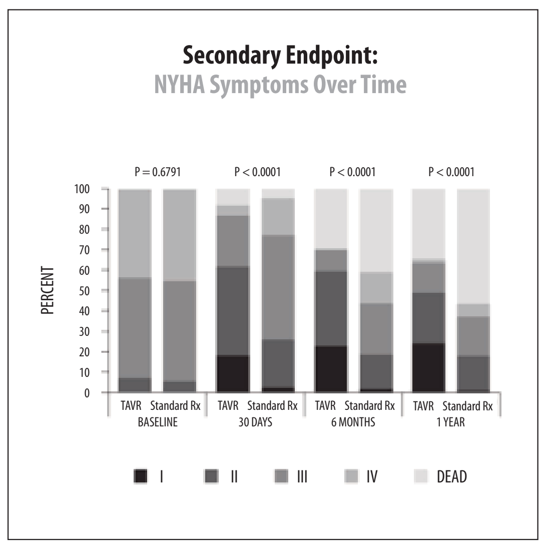


Figure 7

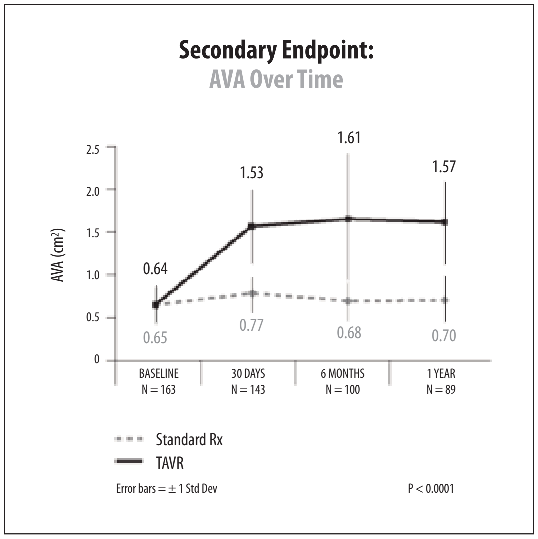


Figure 9

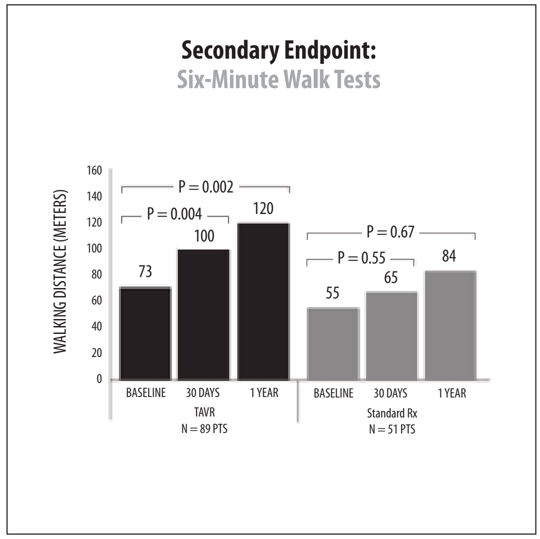


Figure 8

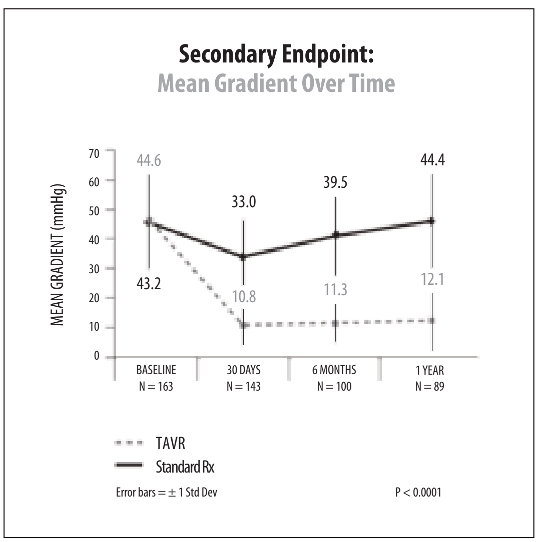


Table 2. Clinical Outcomes at 30 Days and 1 Year (ITT Population)						
	30 Days			1 Year		
Outcome	**Transfemoral TAVR N = 179**	**Standard Care N = 179**	***P*-Value[a]**	**Transfemoral TAVR N = 179**	**Standard Care N = 179**	***P*-Value[a]**
Death						
From any cause	9 (5.0)	5 (2.8)	0.41	55 (30.7)	89 (49.7)	< 0.001
From cardiovascular cause	8 (4.5)	3 (1.7)	0.22	35 (19.6)	75 (41.9)	< 0.001
Repeat hospitalization	10 (5.6)	18 (10.1)	0.17	40 (22.3)	79 (44.1)	< 0.001
Death from any cause or repeat hospitalization	20 (11.2)	22 (12.3)	0.74	78 (43.6)	126 (70.4)	< 0.001
TIA	0	0	-	1 (0.6)	0	1
All Stroke[g]	13 (7.3)	3 (1.7)	0.02	20 (11.2)	8 (4.5)	0.03
Major Stroke	10 (5.6)	2 (1.1)	0.04	15 (8.4)	7 (3.9)	0.12
Myocardial Infarction						
All	0	0	-	1 (0.6)	1 (0.6)	1
Peri-procedural	0	0	-	0	0	-
Hemorrhagic Vascular Complication[h]	90 (50.3)	25 (14.0)	< 0.0001	100 (55.9)	25 (14.0)	< 0.0001
Major Vascular Complication	30 (16.8)	2(1.1)	< 0.0001	31 (17.3)	4 (2.2)	< 0.0001
Renal Failure	2 (1.1)	2 (1.1)	1	4 (2.2)	5 (2.8)	0.59
Renal Insufficiency	1 (0.6)	0 (0.0)	1	2 (1.1)	3 (1.7)	1
Bleeding Event[h]	29 (16.2)	4 (2.2)	< 0.0001	31 (7.3)	4 (2.2)	< 0.0001
Cardiac reintervention						
Balloon aortic valvuloplasty	1 (0.6)[d]	2 (1.1)	1	1 (0.6)	66 (36.9)[e]	< 0.001
Repeat TAVR	3 (1.7)	NA	-	3 (1.7)	NA	-
Aortic-valve replacement	0	3 (1.7)	0.25	2 (1.1)[d]	17 (9.5)	< 0.001
Endocarditis	0	0	-	2 (1.1)	1 (0.6)	0.31
New Atrial Fibrillation	1 (0.6)	2 (1.1)	1	1 (0.6)	3 (1.7)	0.62
New pacemaker	6 (3.4)	9 (5.0)	0.6	8 (4.5)	14 (7.8)	0.27

NA = not applicable, TAVR = transcatheter aortic valve replacement, TIA = transient ischemic attack.
Data presented as n (%) of patients.

a. *p*-values are for between-group comparisons of the frequency of the event at each time point. Analyses were conducted using Fisher's exact test.
b. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
c. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
d. One patient in the TAVR group did not receive TAVR (because of failed access) and subsequently underwent balloon aortic valvuloplasty, followed by aortic-valve replacement.
e. 30 patients underwent repeat BAV after the index BAV procedure that had been performed in the first 30 days after randomization, and 36 patients underwent a first BAV more than 30 days after randomization.
f. Three patients underwent a repeat TAVR within 24 hours after the index TAVR procedure; four patients in the standard of care group who underwent TAVR at a nonparticipating, ex-US site are not included here.
g. Stroke per protocol definition as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 with a brain imaging study showing an infarction
h. Per additional analysis requested by FDA with new definition.

Edwards

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Edwards

RetroFlex Balloon Catheter

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Please verify that you have the latest version of the instructions for use prior to using the device.

1.0 Device Description

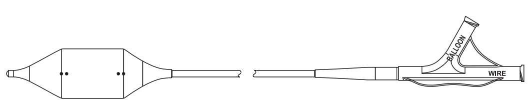
The RetroFlex Balloon Catheter consists of a shaft and balloon with radiopaque markers indicating working length of the balloon. At the proximal end of the device, there is a standard "Y-connector" for balloon inflation and the guidewire lumen. The inflation parameters are as follows:

Table 1. Inflation Parameters

Model	Balloon Dimensions	Inflation Volume
9120BC20	20 mm x 3 cm	13 mL
9120BC23	23 mm x 3 cm	16 mL

RetroFlex Balloon Catheter

THV114



Black dots indicate position of radiopaque markers.

Device Compatibility:

- Maximum guidewire diameter: 0.035" (0.89 mm)
- Minimum sheath compatibility: 14F (4.62 mm)

NOTE: For proper volume sizing, the balloon catheter should be used with the inflation device provided by Edwards Lifesciences.

2.0 Indications

The RetroFlex balloon catheter is indicated for valvuloplasty of a stenotic cardiac valve prior to implantation of a transcatheter heart valve.

3.0 Contraindications

- Other than standard risks associated with insertion of a cardiovascular catheter, there are no known contraindications for valvuloplasty. The patient's medical condition could affect successful use of this catheter.

4.0 Warnings

- The device is designed, intended, and distributed for single use only. **Do not resterilize or reuse the device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.
- Do not mishandle the device or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.

5.0 Precautions

- For special considerations associated with the use of this device prior to transcatheter heart valve implantation, refer to the bioprosthesis Instructions for Use.
- Use only appropriate balloon inflation medium. Do not use air or gaseous medium to inflate the balloon.
- The device is not intended for post-dilatation of deployed transcatheter heart valves.
- While exposed within the body, device advancement and retrieval should not be done without the aid of fluoroscopy. Do not advance or retract the device unless the balloon is fully deflated under vacuum.

6.0 Potential Adverse Events

Complications associated with standard catheterization, balloon valvuloplasty, and the use of angiography include, but are not limited to, allergic reaction to anesthesia or to contrast media, injury including perforation or dissection of vessels, thrombus formation, plaque dislodgement and embolization that may result in myocardial infarction, stroke, distal peripheral occlusion and/or death, arrhythmia development, cardiac perforation, conduction system injury, hematoma, infundibulum injury, annular tear or rupture and/or valve leaflet dehiscence, severe valve insufficiency, valve restenosis, valve damage, balloon rupture.

7.0 Directions for Use

Step	Procedure
1	Prepare vascular access site for valvuloplasty balloon catheter insertion and position guidewire using standard techniques.
2	Flush the valvuloplasty balloon catheter with heparinized saline. Attach a high pressure 3-way stopcock to the balloon inflation port.
3	Prepare a 20 mL syringe with 5 mL diluted contrast solution (15:85 contrast to heparinized saline) and attach to the stopcock.
4	Completely fill the inflation device provided by Edwards with diluted contrast solution and attach in the locked position to the stopcock; close the stopcock to the inflation device.
5	Slowly pull vacuum with the 20 mL syringe repeatedly to remove air, leaving neutral pressure in the system.
6	Close the stopcock to the balloon catheter. Gradually remove contrast medium into the 20 mL syringe to achieve the appropriate volume by rotating the knob of the inflation device. Close the stopcock to the 20 mL syringe and remove the 20 mL syringe from the system.
7	Remove balloon cover and hydrate the length of the balloon catheter.
8	Advance the balloon catheter over the guidewire, through the introducer sheath, across the valve, and position the balloon markers at the intended site.
9	Fully inflate the balloon with the inflation device.
10	Completely deflate the balloon, and gently withdraw the valvuloplasty balloon catheter and remove from the sheath.

8.0 How Supplied

Supplied pouched and sterilized by ethylene oxide.

9.0 Storage

Store in a cool, dry place.

10.0 Device Disposal

Used devices may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

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Edwards

Crimper
Model 9100CR23/ 9100CR26

Instructions for Use

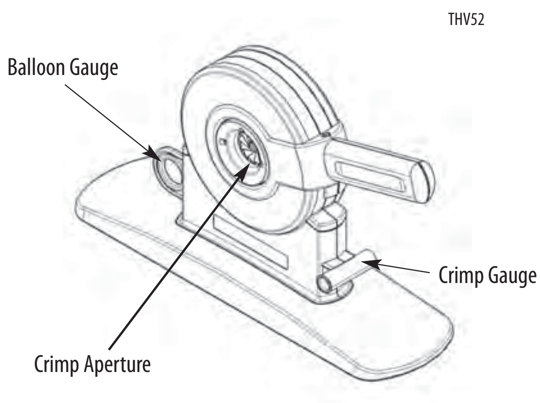
Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Please verify that you have the latest version of the instructions for use prior to using the device.

1.0 Device Description

The Crimper is comprised of a housing and a compression mechanism, creating an aperture that is opened and closed by means of a handle. The Crimper includes a balloon gauge to verify diameter of an inflated balloon catheter. The Crimper is available in two sizes, 23 mm and 26 mm, with a corresponding balloon gauge for each size. It also includes a crimp gauge to verify collapsed diameter of the device.

Figure 1. Crimper



2.0 Indications

The Crimper is indicated for use in preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

3.0 Contraindications

No known contraindications.

4.0 Warnings

- The device is designed, intended, and distributed for single use only. **Do not resterilize or reuse the device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.
- Do not mishandle the device or use it if the packaging or any components are not sterile, have been opened or are damaged, or the expiration date has elapsed.

5.0 Precautions

For special considerations associated with the use of this device prior to transcatheter heart valve implantation, refer to the bioprosthesis Instructions for Use.

6.0 Potential Adverse Events

No known potential adverse events.

7.0 Directions for Use

1. Remove the bioprosthesis from its package and gently place the bioprosthesis into the crimper aperture.
2. Crimp the bioprosthesis by rotating the handle to close the aperture.

8.0 How Supplied

The Crimper is supplied sterilized by ethylene oxide.

9.0 Storage

The Crimper should be stored in a cool, dry place.

10.0 Device Disposal

Used crimpers may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 7,530,253 and corresponding foreign patents. Additional patents are pending.

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APPENDIX B

Morgan Stanley

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April 24, 2013

Stock Rating
Equal-weight

Industry View
In-Line

Edwards Lifesciences

Momentum Transition; Remain Equal Weight

Consecutive disappointments call for thesis re-evaluation and likely range bound near-term performance. A constructive view requires conviction on: (i) reaccelerating growth supported by Japan, Centera and PARTNER II and (ii) leverage to drive faster EPS growth than peers.

The market is simply smaller. Our Equal-weight rating centers on a smaller market size for TAVR than consensus sees. Structural dynamics described on the call highlighted key concerns including less favorable economics at smaller centers and capacity issues in large centers. We struggle to see how these dynamics get better near-term and both suggest market development is taking 1-2 years longer than expected; we forecast WW TAVR market sales of $1.8bn. Our Sapien forecasts go to $705mn from $721mn in '13 and to $900mn from $1bn in '14.

Sometimes you just get what you need. Growth is not proving to be as fast as investors want, but it remains faster than peers'. Japan approval in late '13 and reimbursement in '14, share gains from the Centera launch in Europe in '14 and the PARTNER II Cohort A market expansion in 2014-2016 suggest secular growth rates meaningfully above large cap device peers'.

The momentum thesis is broken, but is EW investable on an EPS basis? In our view, not yet. We are lowering our 2014 EPS est. to $3.87 from $4.16. Stocks never transition from growth to earnings delicately, but there is reason for optimism. R&D is coming down, gross margins should continue to trend higher, and SG&A spend is within management's control. Assuming a ~$72 trading range tomorrow, EW trades at 18-19x '14, which is not compelling but a reasonable support level as investors evaluate growth and EPS opportunities into 2014/15. Our base case goes to $78 from $92.

Key Ratios and Statistics

Reuters: EW.N Bloomberg: EW US
Medical Technology / United States of America

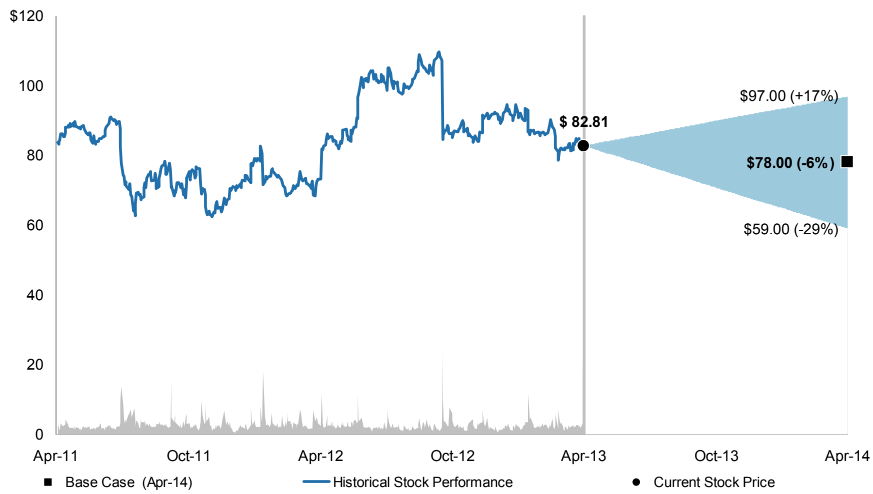
Price target	**NA**
Shr price, close (Apr 23, 2013)	$82.81
Mkt cap, curr (mm)	$9,605
52-Week Range	$110.79-72.50

Fiscal Year ending	**12/11**	**12/12**	**12/13e**	**12/14e**
ModelWare EPS ($)	**2.02**	**2.69**	**3.07**	**3.87**
Prior ModelWare EPS ($)	**-**	**-**	**3.24**	**4.16**
P/E	**35.0**	**33.5**	**27.0**	**21.4**
Consensus EPS ($)§	**1.99**	**2.55**	**3.27**	**3.96**
Div yld (%)	-	-	-	-

Unless otherwise noted, all metrics are based on Morgan Stanley ModelWare framework (please see explanation later in this note).
§ = Consensus data is provided by Thomson Reuters Estimates.
e = Morgan Stanley Research estimates

Risk-Reward Snapshot: Edwards LifeSciences (EW, $82.81, Equal-Weight)

Risk-Reward View



Source: Thomson Reuters, Morgan Stanley Research

Bull Case $97	24x Bull Case 2013e EPS of $3.99	**European TAVR adoption remains robust and US uptake rebounds** with transaortic gains offsetting transapical weakness. Cohort A US uptake proves faster than expected. Core businesses recover to mid-to-high single-digit growth.
Base Case $78	20x Base Case 2014e EPS of $3.87	**European TAVR adoption slows and Sapien cedes share in transapical**. Cohort A US uptake is measured and proves an incremental driver while new center adds remain slower than expected. Core business growth remains in the low single digits.
Bear Case $59	16x Bear Case of 2013e EPS of $3.69	**European TAVR adoption slows and Sapien cedes share in transapical** and transfemoral to MDT/STJ/BSX/Symetis. Cohort A US uptake is slow and reimbursement proves a hurdle for smaller and non-urban centers. Core businesses remain in the low single digits.

Investment Thesis

- Sapien guidance for '13 looks a bit conservative and Edwards likely demonstrates greater leverage in 13' and beyond.
- Beyond '13, consensus for longer-term Sapien growth remains well above our forecasts, which are more conservative on pricing and competition.
- Given likelihood of deceleration into '14 and beyond, we continue to see pipeline upside (particularly mitral) as necessary for share outperformance.
- Absent the pipeline, flattening growth in developed markets in '15-'16 would challenge the implied valuation of the Sapien platform, which we estimate at 5-6x '16 sales.

Potential Catalysts

- Next gen transcatheter valves Sapien 3 and Centera [late '13/'14 launches]
- PARTNER 2 Cohort B headline data [top line potentially at ACC in March '13]
- Sapien approval in Japan [2H13; reimbursement in '14]
- Mitral first in man data [potentially in '13]
- Intuity US launch [2015/2016]

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Exhibit 1

Variance Analysis

			Current Quarter					Y/Y %
(in millions, except EPS)	1Q13E	1Q13A	A vs E (/%)		EPS Impact	Cons.	1Q12A	Change
Revenues:								
Heart Valve Therapy	$210	$198	($12)	-6%	($0.02)	$208	$204	-2.7%
Surg. Heart Valves	$182	$171	($11)	-6%	($0.02)	$179	$176	-2.8%
Card Surg Sys	$29	$27	($2)	-6%	($0.00)	$29	$28	-2.2%
TAVR	$165	$170	$5	3%	$0.01	$171	$122	39.7%
US	$87	$83	($4)	-5%	($0.01)	$91	$41	100.5%
OUS	$78	$87	$9	11%	$0.01	$83	$80	8.2%
Total Cricital Care	$138	$129	($9)	-6%	($0.01)	$138	$134	-3.9%
Critical Care	$126	$115	($11)	-9%	$0.00	$125	$122	-5.3%
Vascular	$12	$14	$2	16%	$0.00	$13	$13	10.4%
Total Revenues	**$513**	**$497**	**($16)**	**-3%**	**($0.02)**	**$519**	**$459**	**8.2%**
FX	**($9)**	($8)	$1					
COGS	$127	$122	($5)	-4%	$0.03		$127	-4%
Gross Profit	**$386**	**$375**	**($12)**	**-3%**		**$388**	**$332**	**13%**
Operating Expenses:								
SG&A	$192	$185	($7)	-3%	$0.04		$177	5%
R&D	$75	$80	$5	7%	($0.03)		$69	16.3%
Total Operating Expenses	**$266**	**$265**	**($1)**	**-1%**	**$0.01**		**$246**	**8%**
Operating Income (Loss)	**$120**	**$110**	**($10)**	**-9%**		**$119**	**$86**	**27%**
Interest Income (Expense)	($0)	$0	$1	--	($0.00)		$0	N/A
Other Income (Expense)	($0)	($1)	($1)	--	($0.00)		($1)	100%
Pretax income	**$120**	**$109**	**($11)**	**-9%**			**$86**	**27%**
Income Taxes	$31	$24	($6)	-21%	$0.03		$23	7%
Net Income (Loss)	**$89**	**$84**	**($5)**	**-5%**			**$63**	**34%**
Diluted Shares Outstanding	117.6	116.5	(1.1)	-1%	$0.01		118.0	-1%
EPS, Diluted	**$0.76**	**$0.72**	**($0.03)**	**-4%**	**($0.03)**	**$0.76**	**$0.53**	**36%**
Margin Analysis								
Gross Profit	75.3%	75.4%	--	10 bps		74.8%	72.3%	310 bps
SG&A	36.4%	36.3%	--	-10 bps			38.6%	-230 bps
R&D	14.5%	16.1%	--	150 bps			14.9%	110 bps
Operating Income	23.4%	22.0%	--	-130 bps		22.9%	18.8%	330 bps
Pre-tax Income	23.3%	21.8%	--	-150 bps			18.6%	320 bps
Tax Rate	25.6%	22.4%	--	-320 bps			26.6%	-420 bps
Net Income	17.3%	17.0%	--	-40 bps			13.7%	330 bps

Source: Company data, Morgan Stanley Research

Details on the Quarter and Updated Forecasts

Exhibit 2
Sapien US Unit Build

	Mar-12	Jun-12	Sep-12	Dec-12	Mar-13	Jun-13	Sep-13	Dec-13
Patients (000)								
High Risk	0.0	0.0	0.0	0.3	0.6	1.0	1.3	1.6
Inoperable	0.8	1.3	1.4	1.6	1.7	1.8	1.8	2.0
Total	0.8	1.3	1.4	1.9	2.4	2.8	3.1	3.6
Avg Centers	65	105	155	192	218	238	258	278
Cases/Ctr/Qtr	12.3	12.4	9.0	10.0	10.8	11.9	12.2	12.9
Ctr Adds/Qtr		40	50	37	26	20	20	20
$ Comm'l Rev.	24	39	42	58	71	85	94	107
Comm'l Revenue Growth Yr/Yr					195%	116%	125%	86%
Centers Trained by Order Added								
1-100	65	100	100	100	100	100	100	100
101-200		5	55	92	100	100	100	100
201+					18	38	58	78
Center Implant Rate per Quarter by Order Added								
1-100	12	12	11	13	14	16	18	18
101-200			5	7	9	11	10	13
201+					3	3	6	6

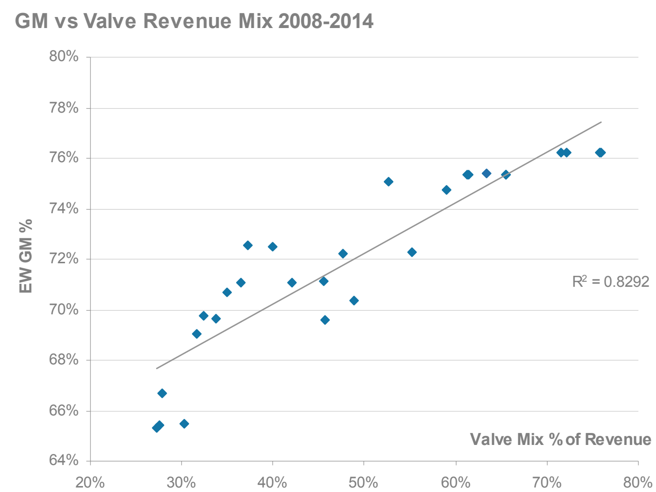
Source: Company Data, Morgan Stanley Research

Exhibit 3
Guidance Tracker

	04-Feb-13	23-Apr-13	MS Current	MS Prior
2013E				
Surgical Valves + Cardiac Surgery Systems	$800-840	$770-810	$784	$809
Sapien THV	$710-$790 (US $390-440mn), up 30-45% ex-FX	$670-$750 (US $350-400mn), up 25-30% ex-FX	*$705*	*$721*
Critical Care + Vasc.	$560-600mn	$530-570mn	$563	$578
FX	-$20mn	-$50mn	-$41	-$22
Total Sales	$2.1-2.2bn (+13-16%)	$2.0-2.1bn	**$2,052**	**$2,109**
Gross Margin	74-76%; 120bps mix impact	74-76%; 120bps mix impact	75.3%	75.3%
SG&A, % sales	36 - 37%	~37%	36.9%	36.5%
R&D	14-16%	~16%	15.6%	15.0%
Tax Rate	23-24%	23%	22.9%	24.1%
Shares out. (mn)	117mn	116mn	116.2	117.3
EPS	$3.21-$3.31	$3.00-$3.10	**$3.07**	**$3.24**

Source: Company data, Morgan Stanley Research

Exhibit 4
Gross Margin vs Valve Mix



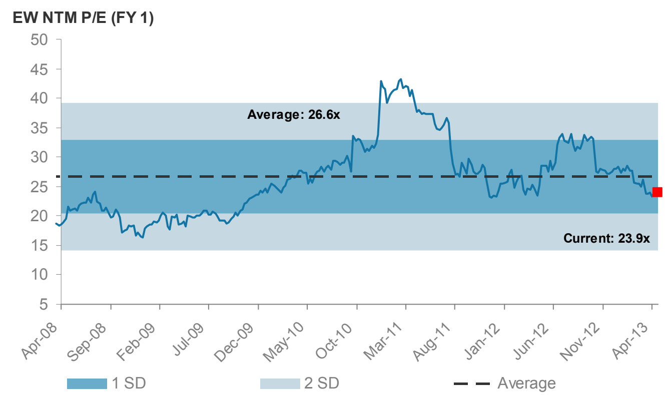
Source: Company Data, Morgan Stanley Research

Exhibit 5
Edwards Base Case Sum of Parts Valuation

	2017 Sales	EV/Sales Multiple	2016 Value	2014 Value	Value per Share
Base Business	1,535	2x	3,069	2,716	23.41
US					
Cohort A	329	5x	1,644	1,280	11.03
Cohort B	341	4x	1,365	1,063	9.16
Europe					
Cohort A	295	5x	1,474	1,148	9.89
Cohort B	185	4x	738	575	4.96
Japan	180	5x	899	700	6.03
Total TAVI	1,329	4.6	6,120	4,765	41.08
Net Cash				1,100	9.48
Total EW	2,864	3.2	9,189	8,581	**$74**

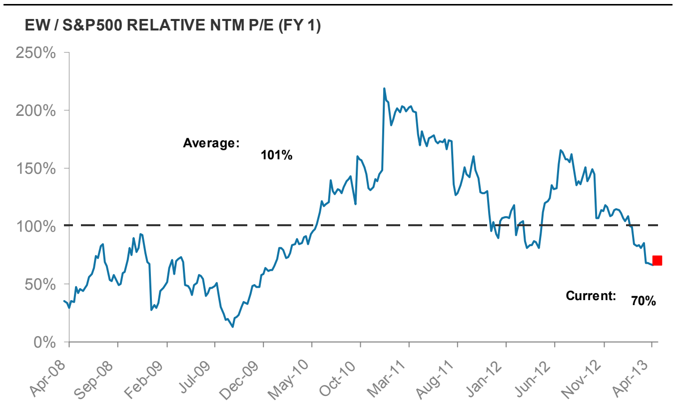
Source: Company data, Morgan Stanley Research

Exhibit 6
EW P/E Trend



Source: Company Data, Morgan Stanley Research

Exhibit 7
EW Relative P/E Trend



Source: Company Data, Morgan Stanley Research

Valuation & Risks

Our 12-month base case valuation for EW is $78. Our base case valuation implies a P/E multiple of ~20x our base Case 2014e EPS, and is in line with our sum of parts valuation. Over half of Edwards' value is associated with the Sapien transcatheter valve program, making valuation on near term forward estimates inappropriate. Our valuation assumes the Sapien program is valued at 4-5x Revenue in 2017, and this value is discounted to 2012 at 8% per year. We value the Edwards base business at 2x EV/Sales.

Risks to our Equal-weight rating include sustained share gains in the surgical and transcatheter heart valve markets, longer-term data from the PARTNER trial, reimbursement and device indications in Europe and the US, a deceleration or decline in US surgical volumes, hospital inventory and pricing pressure, and large-scale dilutive strategic transactions.

Exhibit 8
Edwards Organic Revenue Growth

	Mar-10	Jun-10	Sep-10	Dec-10	Mar-11	Jun-11	Sep-11	Dec-11	Mar-12	Jun-12	Sep-12	Dec-12	Mar-13
Heart Valves	11.6%	20.7%	18.2%	21.6%	23.4%	15.0%	14.0%	12.1%	21.8%	25.4%	22.3%	31.1%	15.2%
Surgical and Repair	4.8%	8.8%	3.9%	5.0%	7.8%	4.2%	1.5%	0.1%	1.9%	(1.0%)	1.5%	5.0%	(1.0%)
Percutaneous	52.0%	99.7%	102.0%	99.1%	88.1%	45.7%	48.0%	22.0%	68.6%	83.0%	65.5%	77.2%	39.7%
Critical Care	7.0%	7.7%	5.5%	3.8%	11.6%	9.0%	7.5%	2.2%	(0.1%)	(1.0%)	2.4%	6.1%	(1.4%)
Cardiac Surgery	7.4%	9.1%	6.8%	6.3%	4.4%	(1.8%)	8.0%	7.5%	5.3%	8.3%	0.4%	8.6%	(2.5%)
Vascular	1.5%	2.3%	6.3%	3.5%	(8.5%)	(8.4%)	(10.3%)	(3.7%)	(3.8%)	(0.8%)	1.6%	7.0%	9.5%
WW Sales	**9.4%**	**14.9%**	**12.6%**	**13.4%**	**17.1%**	**11.1%**	**10.6%**	**8.0%**	**13.3%**	**15.6%**	**14.0%**	**21.2%**	**9.8%**

Source: Company data, Morgan Stanley Research

Exhibit 9

Summary Forecast Changes

	2011	2012	2013E	2014E
Heart Valves (MM)				
Current	1,011	1,228	1,376	1,591
% growth	20.6%	21.5%	12.0%	15.6%
Prior	1,011	1,228	1,415	1,724
% growth	20.6%	21.5%	15.2%	21.8%
TAVR (MM)				
Current	334	552	705	899
% growth	61.6%	65.5%	27.7%	27.6%
Prior	334	552	721	1,008
% growth	61.6%	65.5%	30.6%	39.8%
Total Revenues (MM)				
Current	**1,679**	**1,900**	**2,052**	**2,293**
% growth	**16.0%**	**13.2%**	**8.0%**	**11.8%**
Prior	**1,679**	**1,900**	**2,109**	**2,445**
% growth	**16.0%**	**13.2%**	**11.0%**	**15.9%**
Gross Profit (MM)				
Current	1,189	1,413	1,546	1,748
Gross margin	70.8%	74.4%	75.4%	76.2%
Prior	1,189	1,413	1,588	1,878
Gross margin	70.8%	74.4%	75.3%	76.8%
SG&A (MM)				
Current	642	705	758	826
% of sales	38.3%	37.1%	36.9%	36.0%
Prior	642	705	769	880
% of sales	38.3%	37.1%	36.5%	36.0%
R&D (MM)				
Current	246	291	319	333
% of sales	14.7%	15.3%	15.6%	14.5%
Prior	246	291	315	354
% of sales	14.7%	15.3%	15.0%	14.5%
Interest/Other Income (Expense)				
Current	$ 5	$ (1)	$ (6)	$ (1)
Prior	$ 5	$ (1)	$ (2)	$ (1)
Net Income (MM)				
Current	$ 241	$ 318	$ 357	$ 447
Prior	$ 241	$ 318	$ 381	$ 484
EPS, diluted				
Current	**$2.02**	**$2.69**	**$3.07**	**$3.87**
% growth	**9.9%**	**33.2%**	**14.3%**	**26.1%**
Prior	**$2.02**	**$2.69**	**$3.24**	**$4.16**
% growth	**9.9%**	**33.2%**	**20.7%**	**28.1%**
Diluted Shares Outstanding				
Current	119	118	116	115
Prior	119	118	117	117

Source: Company Data, Morgan Stanley Research

Exhibit 10

Transcatheter Aortic Valve Market Model

TAVI Market Model											
Excludes Clinical Trial Revenue											
WW Total	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
TAVI Market Forecast ($mn)	96	200	387	563	762	1010	1232	1437	1639	1840	1975
EW Market Share	52%	51%	50%	55%	62%	69%	73%	73%	70%	72%	75%
EW TAVI Revenues	50	102	195	307	474	697	904	1048	1142	1329	1480
CoreValve Market Share	48%	49%	50%	45%	33%	25%	14%	14%	18%	16%	14%
Corevalve Revenues	46	98	192	255	251	248	171	206	298	293	268
Other TAVI Market Share	0%	0%	0%	0%	5%	6%	13%	13%	12%	12%	12%
Other Revenues US+EU	0.0	0.0	0.0	0.8	36.7	65.2	157.3	182.7	199.2	217.9	227.3
US	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
Current Surgical AVR Market											
AVR Cases ex TAVI (000)	59	62	65	68	72	75	79	83	87	92	97
Low-Moderate Risk	41	43	45	48	50	53	55	58	61	64	68
High Risk	18	18	19	20	21	23	24	25	26	28	29
Candidates Refused For Surg. AVR	14	15	16	16	17	18	19	20	21	22	23
Impact of TAVI App'l on High Risk Pool	0%	0%	0%	0%	5%	10%	15%	15%	15%	15%	15%
TAVI Indication Penetration											
High Risk	0%	0%	0%	0%	1%	20%	27%	35%	42%	50%	58%
Refused For Surg. AVR	0%	0%	0%	1%	30%	41%	47%	53%	59%	65%	70%
TAVI Procedures											
High Risk	0.0	0.0	0.0	0.0	0.3	4.6	7.4	10.0	12.7	15.8	18.7
Refused For Surg. AVR	0.0	0.0	0.0	0.1	5.1	7.3	10.2	12.1	14.2	16.4	18.3
Total	0.0	0.0	0.0	0.1	5.4	11.9	17.5	22.1	26.9	32.3	37.0
TAVI Market											
TAVI Procedures (000)	0	0	0	0	5	12	18	22	27	32	37
ASP ($000)	$ -	$ -	$ -	$ 30	$ 30	$ 30	$ 29	$ 27	$ 26	$ 24	$ 23
TAVI Sales (mm)	$ -	$ -	$ -	$ 4	$ 163	$ 357	$ 500	$ 599	$ 692	$ 788	$ 858
EW Market Share	100%	100%	100%	100%	100%	100%	100%	90%	80%	85%	90%
EW TAVI Revenues	0	0.0	0.0	3.7	162.8	357.0	499.6	539.3	553.7	670.0	772.4
CoreValve Market Share	0%	0%	0%	0%	0%	0%	0%	10%	20%	15%	10%
Corevalve Revenues	0.0	0.0	0.0	0.0	0.0	0.0	0.0	59.9	138.4	118.2	85.8
Europe	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
Current Surgical AVR Market											
AVR Cases ex TAVI (000)	59	61	65	68	71	75	78	82	86	91	95
Low-Moderate Risk	41	43	45	47	50	52	55	58	61	64	67
High Risk	18	18	19	20	21	22	24	25	26	27	29
Candidates Refused For Surg. AVR	14	15	15	16	17	18	19	20	21	22	23
Impact of TAVI App'l on High Risk Pool	3%	5%	10%	12%	15%	15%	15%	15%	15%	15%	15%
TAVI Indication Penetration											
High Risk	10%	23%	37%	50%	60%	56%	60%	65%	68%	72%	72%
Refused For Surg. AVR	12%	26%	42%	53%	65%	58%	66%	70%	70%	72%	72%
TAVI Procedures											
High Risk	1.8	4.3	7.2	10.1	12.9	14.8	16.3	18.4	20.3	22.4	23.7
Refused For Surg. AVR	1.6	3.8	6.5	8.7	11.1	12.4	14.2	15.8	16.8	18.0	19.0
Total	3.5	8.1	13.7	18.8	23.9	27.2	30.5	34.6	40.2	46.7	51.9
TAVI Market											
TAVI Procedures (000)	3.5	8.1	13.7	18.8	23.9	27.2	30.5	34.6	40.2	46.7	51.9
ASP (Euros 000)	19.0	17.9	20.0	21.4	19.5	18.3	17.2	16.2	15.2	14.3	13.5
TAVI Sales ($US mm)	$ 96	$ 200	$ 387	$ 559	$ 599	$ 652	$ 684	$ 731	$ 797	$ 872	$ 909
EW Market Share	52%	51%	50%	54%	52%	52%	52%	55%	55%	55%	55%
EW TAVI Revenues	50	102.0	194.9	302.9	311.3	339.0	355.7	401.9	438.3	479.3	500.2
CoreValve Market Share	48%	49%	50%	46%	42%	38%	25%	20%	20%	20%	20%
Corevalve Revenues	46.2	98.0	191.8	255.2	251.5	247.7	171.0	146.1	159.4	174.3	181.9
Japan	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
TAVI Sales (mm)	$ -	$ -	$ -	$ -	$ -	$ 1	$ 49	$ 107	$ 150	$ 180	$ 208
Y-Y $ Growth	$ -	$ -	$ -	$ -	$ -	$ 1	$ 48	$ 58	$ 43	$ 30	$ 28
EW Market Share	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%
EW TAVI Revenues	0	0.0	0.0	0.0	0.0	1.1	48.8	107.1	149.9	179.8	207.7
Corevalve Market Share	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Corevalve Revenues	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Source: Company data, Morgan Stanley Research

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Exhibit 11

Income Statement

Dollars in millions, except per share data
Fiscal year ends Dec 31

	2009A	2010A	2011A	2012E					2013E					2014E
				Mar-12	Jun-12	Sep-12	Dec-12		Mar-13	Jun-13	Sep-13	Dec-13		
Total Revenue	**$1,321.4**	**$1,447.0**	**$1,678.6**	**$459.2**	**$482.0**	**$447.9**	**$510.5**	**$1,899.6**	**$496.7**	**$517.7**	**$499.1**	**$538.4**	**$2,051.8**	**$2,293.2**
COGS	399.1	408.3	489.8	127.3	121.7	111.7	125.8	486.5	122.2	127.6	123.1	132.7	505.7	545.3
Gross Profit	**922.3**	**1,038.7**	**1,188.8**	**331.9**	**360.3**	**336.2**	**384.7**	**1,413.1**	**374.5**	**390.0**	**376.0**	**405.6**	**1,546.2**	**1,747.9**
SG&A	508.8	550.0	642.4	177.2	182.4	167.8	177.9	705.3	185.2	191.5	184.7	196.5	757.9	825.6
R&D	175.5	204.4	246.3	68.6	74.0	73.8	74.9	291.3	79.8	79.7	78.9	80.8	319.1	332.5
Total Operating Expenses	684.3	754.4	888.7	245.8	256.4	241.6	252.8	996.6	265.0	271.3	263.5	277.3	1,077.0	1,158.1
EBIT	**238.0**	**284.3**	**300.1**	**86.1**	**103.9**	**94.6**	**131.9**	**416.5**	**109.5**	**118.8**	**112.5**	**128.4**	**469.1**	**589.9**
Interest Income (Expense)	(1.1)	(1.5)	0.3	0.0	0.1	0.3	0.0	0.4	0.2	(0.7)	(0.7)	(0.3)	(1.4)	(1.5)
Other	3.7	8.1	4.8	(0.5)	1.0	(1.5)	(0.7)	(1.7)	(1.2)	(1.2)	(1.2)	(1.2)	(4.8)	0.0
Total Non-Operating Income (ex	2.6	6.6	5.1	(0.5)	1.1	(1.2)	(0.7)	(1.3)	(1.0)	(1.9)	(1.9)	(1.5)	(6.2)	(1.5)
Pretax Income	**240.6**	**290.9**	**305.2**	**85.6**	**105.0**	**93.4**	**131.2**	**415.2**	**108.5**	**116.9**	**110.6**	**126.9**	**462.9**	**588.4**
Income Tax Expense	58.5	72.0	64.2	22.8	25.5	24.2	24.7	97.2	24.3	26.9	25.4	29.2	105.8	141.2
Income Tax Rate	24.3%	24.7%	21.0%	26.6%	24.3%	25.9%	18.8%	23.4%	22.4%	23.0%	23.0%	23.0%	22.9%	24.0%
Net Income	**182.1**	**218.9**	**241.0**	**62.8**	**79.5**	**69.2**	**106.5**	**318.0**	**84.2**	**90.0**	**85.2**	**97.7**	**357.1**	**447.2**
Quality of Income	0.9	1.1	1.3	(0.5)	1.8	1.9	1.2	1.2	(1.8)	1.6	0.9	6.2	1.7	1.3
Diluted Shares Outstanding	117.4	119.2	119.4	118.0	118.4	119.0	117.8	118.3	116.5	116.3	116.1	115.9	116.2	115.4
Diluted EPS, adjusted	**$1.55**	**$1.84**	**$2.02**	**$0.53**	**$0.67**	**$0.58**	**$0.90**	**$2.69**	**$0.72**	**$0.77**	**$0.73**	**$0.84**	**$3.07**	**$3.87**
Margins/Expense:														
Total Cost of Goods Sold	30.2%	28.2%	29.2%	27.7%	25.2%	24.9%	24.6%	25.6%	24.6%	24.7%	24.7%	24.7%	24.6%	23.8%
Gross Profit	69.8%	71.8%	70.8%	72.3%	74.8%	75.1%	75.4%	74.4%	75.4%	75.3%	75.3%	75.3%	75.3%	76.2%
SG&A Base	38.5%	38.0%	38.3%	38.6%	37.8%	37.5%	34.8%	37.1%	36.3%	36.0%	36.0%	35.5%	36.9%	35.0%
Med Tech Tax									1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
R&D	13.3%	14.1%	14.7%	14.9%	15.4%	16.5%	14.7%	15.3%	16.1%	15.4%	15.8%	15.0%	15.6%	14.5%
Total Operating Expenses	51.8%	52.1%	52.9%	53.5%	53.2%	53.9%	49.5%	52.5%	53.4%	52.4%	52.8%	51.5%	52.5%	50.5%
EBIT	18.0%	19.6%	17.9%	18.8%	21.6%	21.1%	25.8%	21.9%	22.0%	22.9%	22.5%	23.8%	22.9%	25.7%
Pretax Income	18.2%	20.1%	18.2%	18.6%	21.8%	20.9%	25.7%	21.9%	21.8%	22.6%	22.2%	23.6%	22.6%	25.7%
Net Income (excl. 1x charges)	13.8%	15.1%	14.4%	13.7%	16.5%	15.4%	20.9%	16.7%	17.0%	17.4%	17.1%	18.1%	17.4%	19.5%
Growth Analysis:														
Total revenue	6.8%	9.5%	16.0%	13.5%	11.8%	8.5%	18.7%	13.2%	8.2%	7.4%	11.4%	5.5%	8.0%	11.8%
Revenue (Ex-FX, M&A)	8.5%	12.6%	11.5%	13.3%	15.6%	14.0%	21.2%	16.1%	9.8%	10.2%	13.5%	8.4%	10.4%	12.1%
Total Cost of Goods Sold	-5.9%	2.3%	20.0%	9.0%	-4.8%	-11.1%	5.2%	-0.7%	-4.0%	4.9%	10.2%	5.5%	3.9%	7.8%
SG&A	5.9%	8.1%	16.8%	17.9%	11.8%	1.4%	8.9%	9.8%	4.5%	5.0%	10.0%	10.5%	7.5%	8.9%
R&D	26.1%	16.5%	20.5%	16.3%	14.0%	19.6%	23.4%	18.3%	16.3%	7.7%	6.9%	7.8%	9.6%	4.2%
Operating Expenses	10.4%	10.2%	17.8%	17.4%	12.4%	6.3%	12.8%	12.1%	7.8%	5.8%	9.1%	9.7%	8.1%	7.5%
EBIT	22.7%	19.5%	5.5%	9.8%	38.0%	57.9%	52.5%	38.8%	27.2%	14.3%	18.9%	-2.7%	12.6%	25.7%
EPS	25.0%	18.4%	9.9%	0.4%	36.1%	54.8%	45.9%	33.2%	35.8%	15.3%	26.2%	-6.8%	14.3%	26.1%

Source: Company data, Morgan Stanley Research

Exhibit 12

Revenue Build

Dollars in millions, except per share data
Fiscal year ends Dec 31

	2009A	2010A	2011A	2012E Mar-12	2012E Jun-12	2012E Sep-12	2012E Dec-12	2012E	2013E Mar-13	2013E Jun-13	2013E Sep-13	2013E Dec-13	2013E	2014E	2015E
WW Sales	**$1,321**	**$1,447**	**$1,679**	**$459.2**	**$482**	**$448**	**$511**	**$1,900**	**$497**	**$518**	**$499**	**$538**	**$2,052**	**$2,293**	**$2,483**
y/y growth, reported	*6.8%*	*9.5%*	*16.0%*	*13.5%*	*11.8%*	*8.5%*	*18.7%*	*13.2%*	*8.2%*	*7.4%*	*11.4%*	*5.5%*	*8.0%*	*11.8%*	*8.3%*
Disc'd Ops/Other impact	(45)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Underlying Sales	1,277	1,447	1,679	*459*	*482.0*	*447.9*	*510.5*	1,900	*497*	*518*	*499*	*538*	2,052	2,293	2,483
FX Impact ($)	(16)	9	58	0.7	(14.4)	(19.8)	(8.9)	(42)	(6.7)	(12)	(8)	(14)	(41)	(7)	0
y/y organic growth CC	*8.5%*	*12.6%*	*11.5%*	*13.3%*	*15.6%*	*14.0%*	*21.2%*	*16.1%*	*9.8%*	*10.2%*	*13.5%*	*8.4%*	*10.4%*	*12.1%*	*8.3%*
Ex TAVR	*3.4%*	*5.3%*	*2.8%*	*1.0%*	*0.2%*	*0.9%*	*4.4%*	*3.1%*	*-0.7%*	*3.5%*	*3.3%*	*3.1%*	*2.4%*	*2.7%*	*2.0%*
Ex US TAVR	*7.9%*	*12.5%*	*9.7%*	*4.1%*	*2.9%*	*2.5%*	*6.4%*	*4.0%*	*0.7%*	*4.0%*	*5.9%*	*4.2%*	*3.7%*	*6.0%*	*6.2%*
Heart Valve Therapy															
Annuloplasty Rings	97	103	116	33	24	22	21	100	33	24	22	21	100	103	105
y/y growth	*-3.9%*	*5.6%*	*13.1%*	*3.1%*	*-20.6%*	*-22.9%*	*-17.8%*	*-10.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*3.0%*	*2.0%*
Mechanical/Other	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
y/y growth	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Tissue	501	529	561	143	148	138	148	576	138	150	139	143	571	588	606
y/y growth	*9.5%*	*5.6%*	*6.0%*	*2.0%*	*0.0%*	*2.0%*	*7.0%*	*2.7%*	*-3.0%*	*2.0%*	*1.0%*	*-3.0%*	*-0.9%*	*3.0%*	*3.0%*
Surg Valves	**598**	**632**	**677**	**176**	**172**	**160**	**169**	**676**	**171**	**175**	**161**	**164**	**671**	**691**	**711**
y/y growth	*7.1%*	*5.6%*	*7.2%*	*2.2%*	*-3.5%*	*-2.3%*	*3.2%*	*-0.2%*	*-2.8%*	*1.7%*	*0.9%*	*-2.6%*	*-0.7%*	*3.0%*	*2.9%*
Est CC	*7.6%*	*5.7%*	*3.2%*	*1.9%*	*-1.0%*	*1.5%*	*5.0%*	*2.4%*	*-1.0%*	*4.2%*	*2.7%*	*0.1%*	*1.4%*	*3.3%*	*2.9%*
Percutaneous	112	206	334	122	146	124	161	552	170	178	169	188	705	899	1,044
y/y growth	124.5%	83.6%	61.6%	67.1%	71.5%	49.9%	72.7%	65.5%	39.7%	22.0%	36.8%	16.8%	27.7%	27.6%	16.1%
Est FX	-2.6%	1.3%	8.0%	-1.5%	-6.6%	-15.6%	-4.5%	-5.1%	0.0%	-5.1%	-3.7%	-5.5%	-4.3%	-0.7%	0.0%
FX $		(3)		(1.1)	(5.6)	(12.9)	(4.2)		0.0						
Est CC	127.1%	90.6%	53.6%	68.6%	83.0%	65.5%	77.2%	70.6%	39.7%	27.1%	40.5%	22.3%	32.0%	28.2%	16.1%
US	6	8	35	41	61	55	81	238	83	91	89	102	365	492	539
y/y growth	NM	24.8%	333.0%	935.0%	916.7%	591.3%	374.7%	581.1%	100.5%	48.7%	61.3%	26.7%	53.2%	34.7%	9.5%
OUS	106	198	299	80	85	69	80	314	87	87	80	86	340	408	506
y/y growth	*111.5%*	*87.2%*	*50.5%*	*16.6%*	*7.3%*	*-8.2%*	*5.4%*	*5.1%*	*8.2%*	*2.9%*	*17.0%*	*6.9%*	*8.4%*	*19.9%*	*24.1%*
Heart Valves	**714.9**	**838.3**	**1,010.7**	**297.5**	**317.6**	**283.5**	**329.6**	**1,228.2**	**340.8**	**352.7**	**330.4**	**352.3**	**1,376.2**	**1,590.6**	**1,755.3**
y/y growth, reported	*17.7%*	*17.3%*	*20.6%*	*21.5%*	*20.7%*	*15.2%*	*28.4%*	*21.5%*	*14.6%*	*11.0%*	*16.6%*	*6.9%*	*12.0%*	*15.6%*	*10.4%*
Disc'd Ops/Other impact	-4	0	0	*0*	*0*	*0*	*0*	0	*0*	*0*	*0*	*0*	0	0	0
FX Impact ($)	*-9*	*-1*	*34*	*-1*	*-10*	*-14*	*-5*	*-30*	*-2*	*-8*	*-5*	*-9*	*-25*	*-5*	*0*
y/y organic growth CC	*17.8%*	*18.1%*	*15.9%*	*21.8%*	*25.4%*	*22.3%*	*31.1%*	*25.2%*	*15.2%*	*14.0%*	*18.8%*	*9.9%*	*14.3%*	*16.0%*	*10.4%*
ex US TAVR	*16.8%*	*17.9%*	*12.7%*	*6.5%*	*4.5%*	*3.1%*	*6.2%*	*5.1%*	*1.3%*	*4.7%*	*6.9%*	*3.4%*	*4.0%*	*6.8%*	*7.4%*
Critical Care															
Hemodynamic Monitoring	237	261	284	66	70	75	91	303	72	71	76	95	314	333	350
y/y growth	*3.0%*	*10.1%*	*8.8%*	*0.0%*	*8.0%*	*9.0%*	*9.0%*	*6.7%*	*9.0%*	*1.0%*	*2.0%*	*4.0%*	*3.9%*	*6.0%*	*5.0%*
FloTrac	62	67	64	17	15	15	15	62	15	15	15	15	60	63	65
y/y growth	*41.6%*	*8.0%*	*-4.4%*	*0.0%*	*0.0%*	*-6.3%*	*-6.3%*	*-3.1%*	*-11.8%*	*0.0%*	*1.0%*	*2.0%*	*-2.5%*	*4.0%*	*3.0%*
Pressure Monitoring	152	162	191	48	44	42	37	171	35	44	42	37	158	164	171
y/y growth	*7.3%*	*6.4%*	*18.1%*	*2.0%*	*-18.6%*	*-15.7%*	*-8.5%*	*-10.7%*	*-27.0%*	*0.0%*	*0.0%*	*0.0%*	*-7.6%*	*4.0%*	*4.0%*
Hemofiltration	34	-	-	-	-	-	-	-	-	-	-	-	-	-	-
y/y growth	*-35.1%*	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Central Venous Access	30	32	34	8	9	9	10	35	8	9	9	11	36	37	38
y/y growth	*7.1%*	*7.1%*	*6.4%*	*1.0%*	*5.0%*	*6.0%*	*6.0%*	*4.6%*	*6.0%*	*0.0%*	*3.0%*	*2.0%*	*2.6%*	*3.0%*	*3.0%*
Critical Care	**452.5**	**454.1**	**508.3**	**121.6**	**123.2**	**125.6**	**138.0**	**508.4**	**115.1**	**123.9**	**127.4**	**141.9**	**508.2**	**534.5**	**558.8**
y/y growth, reported	*0.2%*	*0.4%*	*7.0%*	*0.8%*	*-3.5%*	*-0.9%*	*3.5%*	*0.0%*	*-5.3%*	*0.6%*	*1.4%*	*2.8%*	*0.0%*	*5.2%*	*4.6%*
Disc'd Ops/Other impact	*(32)*			*0*	*0*	*0*	*0*		*0*						
FX Impact ($)	*(4)*	*9*	*19*	*1*	*(3)*	*(4)*	*(3)*	*-9*	*(5)*	*-3*	*-2*	*-4*	*-14*	*-2*	*0*
y/y organic growth CC	*0.0%*	*6%*	*9.7%*	*-0.1%*	*-1.0%*	*2.4%*	*6.1%*	*4%*	*-1%*	*3%*	*3%*	*6%*	*5%*	*8%*	*7%*
Cardiac Surgery															
Cannulae/Embol-X/Other	69	74	79	20	24	20	21	85	20	25	20	21	86	88	90
y/y growth	*3.1%*	*7.0%*	*7.1%*	*2.0%*	*11.0%*	*6.0%*	*10.0%*	*7.4%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*
CardioVations	24	27	29	8	5	6	8	27	7	5	6	9	27	28	29
y/y growth	*7.4%*	*11.0%*	*7.9%*	*16.4%*	*-17.6%*	*-25.5%*	*0.1%*	*9.0%*	*8.0%*	*4.0%*	*8.0%*	*4.0%*	*0.0%*	*5.0%*	*3.0%*
Cardiac Surgery	**92.8**	**100.2**	**107.5**	**27.6**	**28.7**	**26.0**	**29.1**	**111.4**	**27.0**	**29.4**	**26.9**	**29.8**	**113.1**	**116.2**	**118.8**
y/y growth, reported	*4.0%*	*8.0%*	*7.0%*	*5.7%*	*5.1%*	*-3.3%*	*7.0%*	*3.6%*	*-2.2%*	*2.3%*	*3.4%*	*2.6%*	*1.5%*	*2.7%*	*2.2%*
Disc'd Ops/Other impact	*(0)*			*0*	*0*	*0*	*0*		*0*						
FX Impact ($)	*0*	*1*	*3*	*0*	*(1)*	*(1)*	*(0)*	*-2*	*0*	*-1*	*0*	*-1*	*-2*	*0*	*0*
y/y organic growth CC	*4.2%*	*7.4%*	*4.4%*	*5.3%*	*8.3%*	*0.4%*	*8.6%*	*5.7%*	*-2.5%*	*4.8%*	*5.2%*	*5.4%*	*3.2%*	*3.0%*	*2.2%*
Vascular															
Clot management	32	35	35	8	9	9	9	35	9	8	8	8	34	30	27
y/y growth	*5.5%*	*9.0%*	*2.7%*	*-10.0%*	*8.0%*	*0.0%*	*0.0%*	*-0.6%*	*12.9%*	*-10.0%*	*-10.0%*	*-10.0%*	*-4.8%*	*-10.0%*	*-10.0%*
Atraumatic occlusion/Other	29	23	21	5	3	6	6	20	5	3	6	6	21	22	23
y/y growth	*-49.7%*	*-22.0%*	*-10.3%*	*12.0%*	*-28.5%*	*0.0%*	*0.0%*	*-3.9%*	*6.0%*	*5.0%*	*5.0%*	*5.0%*	*5.2%*	*5.0%*	*5.0%*
Vascular	**61.2**	**54.4**	**52.1**	**12.5**	**12.5**	**12.8**	**13.8**	**51.6**	**13.8**	**11.7**	**14.4**	**14.4**	**54.3**	**52.0**	**50.1**
y/y growth, reported	*-31.5%*	*-11.1%*	*-4.2%*	*-3.1%*	*-4.6%*	*-1.5%*	*5.3%*	*-1.0%*	*10.4%*	*-6.1%*	*12.5%*	*4.3%*	*5.3%*	*-4.3%*	*-3.7%*
Disc'd Ops/Other impact	*(8)*			*0*	*0*	*0*	*0*		*0*						
FX Impact ($)	*(4)*	*0*	*2*	*0*	*(1)*	*(0)*	*(0)*	*-1*	*0*	*0*	*0*	*0*	*-1*	*0*	*0*
y/y organic growth CC	*-0.9%*	*2.4%*	*-7.8%*	*-3.8%*	*-0.8%*	*1.6%*	*7.0%*	*1.0%*	*9.5%*	*-4.0%*	*14.6%*	*7.3%*	*6.9%*	*-4.0%*	*-3.7%*

Source: Company data, Morgan Stanley Research

Exhibit 13

Balance Sheet

Dollars in millions, except per share data

Fiscal year ends Dec 31

	2007A	2008A	2009A	2010A	2011A	2012E	2013E	2014E	2015E
ASSETS									
Cash and Equivalents	$141.8	$218.7	$334.1	$396.1	$171.3	$311.0	$661.1	$930.0	$1,256.3
Short-term Investments	49.4	8.1	0.0	0.0	279.3	210.5	210.5	210.5	210.5
Accounts Receivables	115.8	186.3	249.4	277.3	283.8	347.5	355.1	397.6	426.6
Other Receivables	29.5	18.4	22.7	25.2	36.9	9.9	9.9	9.9	9.9
Inventories	152.6	151.8	165.9	203.6	261.3	281.0	290.0	313.1	331.6
Deferred Income Taxes	30.2	42.4	48.3	51.9	43.9	43.4	43.4	43.4	43.4
Prepaid Expenses and Other CA	62.4	66.2	68.8	78.5	92.1	98.6	54.6	60.7	65.0
- Prepaid expenses	25.4	30.7	33.7	35.4	35.0	41.6	43.8	49.0	52.6
- Other current assets	37.0	35.5	35.1	43.1	57.1	57.0	10.8	11.7	12.3
Total Current Assets	**581.7**	**691.9**	**889.2**	**1,032.6**	**1,168.6**	**1,301.9**	**1,624.7**	**1,965.2**	**2,343.3**
PPE, net	228.2	230.1	252.0	269.8	304.3	373.3	405.5	440.6	477.3
Goodw ill	350.3	315.7	315.2	315.2	349.8	384.7	384.7	384.7	384.7
Other Intangible Assets, net	122.5	96.9	86.7	67.1	66.9	67.0	74.4	82.1	90.2
Investments in unconsol. Affiliates	34.3	14.7	22.3	25.0	21.8	21.1	21.1	21.1	21.1
Deferred Income Taxes	13.8	37.7	37.1	44.5	20.0	47.3	47.3	47.3	47.3
Other Assets	14.3	13.2	13.0	13.0	49.2	26.3	26.3	26.3	26.3
Total Assets	**$1,345.1**	**$1,400.2**	**$1,615.5**	**$1,767.2**	**$1,980.6**	**$2,221.6**	**$2,583.9**	**$2,967.2**	**$3,390.2**
LIABILITIES									
AP and Accrued Liabilities	$225.4	$258.5	$290.5	$296.0	$335.2	$347.4	$429.8	$464.0	$491.4
Short-term Debt	0.0	0.0	0.0	41.8	0.0	0.0	0.0	0.0	0.0
Total Current Liabilities	**225.4**	**258.5**	**290.5**	**337.8**	**335.2**	**347.4**	**429.8**	**464.0**	**491.4**
Long-term Debt	211.7	175.5	90.3	0.0	150.4	189.3	180.3	180.3	180.3
Other Long-term Liabilities	73.0	87.4	76.8	121.2	157.0	205.5	214.5	214.5	214.5
Commitments & Contingencies	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Liabilities	**510.1**	**521.4**	**457.6**	**459.0**	**642.6**	**742.2**	**824.6**	**858.8**	**886.2**
EQUIITY									
Common Stock	68.6	73.7	76.1	117.0	120.0	124.2	124.2	124.2	124.2
Additional Contributed Capital	680.6	940.4	1,056.0	211.3	300.5	489.0	728.7	1,008.8	1,328.5
Retained Earnings	548.6	676.9	906.0	1,124.0	1,360.7	1,653.9	2,071.7	2,518.8	3,034.2
Accumulated Other Compre. Income	7.5	(35.4)	(7.9)	(42.1)	(37.5)	(37.9)	(37.9)	(37.9)	(37.9)
Treasury Stock	(470.3)	(776.8)	(872.3)	(102.0)	(405.8)	(749.9)	(1,066.8)	(1,444.9)	(1,884.5)
Total Stockholders' Equity	835.0	878.8	1,157.9	1,308.2	1,337.9	1,479.3	1,819.9	2,169.1	2,564.6
Total Liabilities & Equity	**$1,345.1**	**$1,400.2**	**$1,615.5**	**$1,767.2**	**$1,980.5**	**$2,221.5**	**$2,644.5**	**$3,027.8**	**$3,450.8**

Source: Company data, Morgan Stanley Research

Exhibit 14

Cash Flow Statement

Dollars in millions, except per share data
Fiscal year ends Dec 31

	2007A	2008A	2009A	2010A	2011A	2012E	2013E	2014E	2015E
OPERATING									
GAAP Net Income	$113.0	$128.9	$229.1	$218.0	$236.7	$293.2	$357.1	$447.2	$515.4
Depreciation & Amortization	54.8	55.6	58.7	56.5	58.0	57.3	97.6	110.1	120.0
Deferred income taxes	(5.6)	(23.5)	(4.0)	(11.2)	(0.6)	8.1	0.0	0.0	0.0
Purchased IPR&D	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Special charges	14.9	25.4	(75.5)	22.7	21.2	14.9	0.0	0.0	0.0
Stock Compensation Expense	27.7	28.7	28.3	29.3	29.0	42.1	49.5	53.3	56.0
Other	1.3	7.6	(3.0)	(62.8)	(0.1)	(53.3)	0.0	0.0	0.0
Net Change in Working Capital	4.1	(69.5)	(68.3)	(1.1)	(29.7)	11.5	109.7	(37.4)	(24.4)
Cash from Operations	**210.2**	**153.2**	**165.3**	**251.4**	**314.5**	**373.8**	**613.9**	**573.1**	**667.0**
INVESTING									
Acquisitions	0.0	0.0	0.0	0.0	(42.6)	(36.6)	0.0	0.0	0.0
Capital expenditures	(57.0)	(50.6)	(64.0)	(61.8)	(82.9)	(120.7)	(129.7)	(145.2)	(156.7)
Investments in intangible assets	(5.5)	(27.4)	0.0	(1.2)	(7.7)	(7.0)	(7.4)	(7.7)	(8.1)
Investments in unconsolidated affiliates	(2.3)	4.4	(3.5)	(4.7)	6.8	0.8	0.0	0.0	0.0
Proceeds from assets dispositions	7.2	97.0	97.9	6.6	3.9	3.0	0.0	0.0	0.0
Proceeds from sale of business	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	(86.9)	35.5	9.7	(0.4)	3.1	(0.6)	0.0	0.0	0.0
Proceeds from notes receivable	0.0	0.0	0.0	0.0	(293.4)	70.6	0.0	0.0	0.0
Net from Investing	**(144.5)**	**58.9**	**40.1**	**(61.5)**	**(412.8)**	**(90.5)**	**(137.1)**	**(152.9)**	**(164.8)**
FINANCING									
Proceeds from issuance of long-term debt	57.3	0.0	129.3	254.4	(421.7)	407.0	0.0	0.0	0.0
Payments on long-term debt	(85.2)	(112.1)	(213.9)	(302.8)	526.1	(367.5)	0.0	0.0	0.0
Proceeds from issuance of short-term debt	0.0	206.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Payments on short-term debt	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Change in Equity, Net of Tax Benefit	(92.2)	(242.7)	(28.8)	(52.8)	(237.9)	(187.5)	(126.8)	(151.2)	(175.8)
Payments relating to AR securitization, net	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	12.0	14.4	21.6	(2.7)	(1.7)	(7.6)	0.0	0.0	0.0
Net from Financing	**(108.1)**	**(134.1)**	**(91.8)**	**(103.9)**	**(135.2)**	**(155.6)**	**(126.8)**	**(151.2)**	**(175.8)**
Effect of currency exchange	1.4	(1.0)	1.8	(24.0)	8.6	12.0	0.0	0.0	0.0
Net Cash Flow	**($41.0)**	**$77.0**	**$115.4**	**$62.0**	**($224.9)**	**$139.7**	**$350.1**	**$269.0**	**$326.3**
Cash Balance	141.8	218.8	334.2	396.2	171.3	311.0	661.1	930.0	1,256.3

Source: Company data, Morgan Stanley Research

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Total	**2,853**		**1022**		

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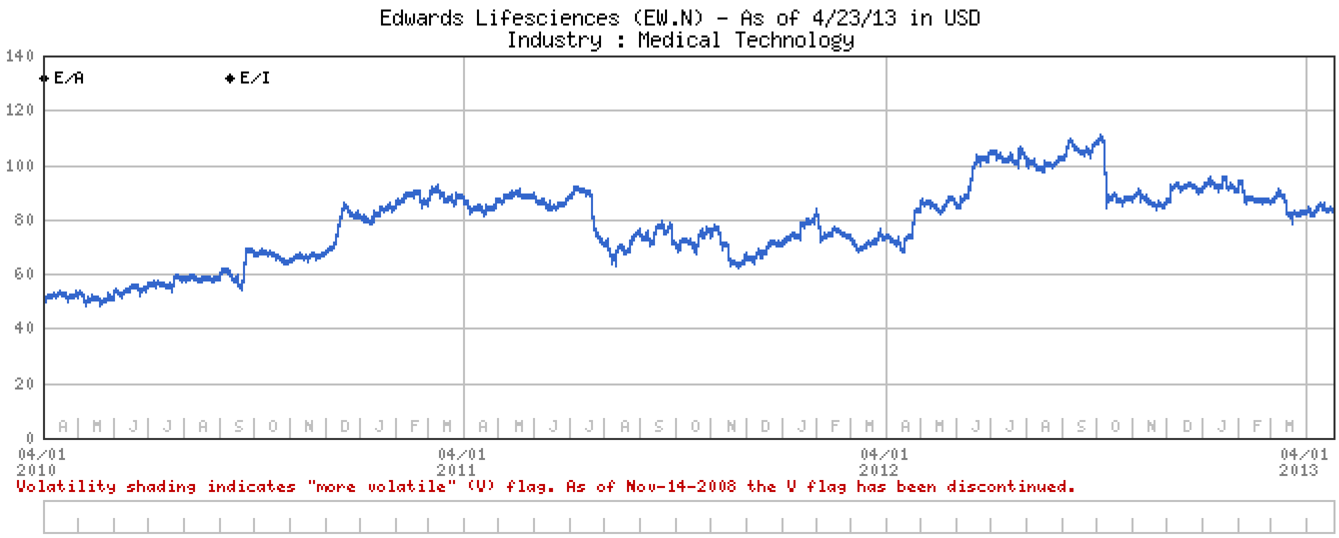
Stock Price, Price Target and Rating History (See Rating Definitions)



Stock Rating History: 4/1/10 : E/A; 9/10/10 : E/I

Price Target History: No Price Target Assigned (NA)

Source: Morgan Stanley Research   Date Format : MM/DD/YY   Price Target -- No Price Target Assigned (NA)
Stock Price (Not Covered by Current Analyst)   Stock Price (Covered by Current Analyst)
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Stock Ratings: Overweight (O) Equal-weight (E) Underweight (U) Not-Rated (NR) More Volatile (V) No Rating Available (NA)
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Company (Ticker)	Rating (as of)	Price* (04/23/2013)
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Align Technology Inc (ALGN.O)	E (01/03/2013)	$31.99
Dentsply International Inc. (XRAY.O)	E (09/12/2011)	$41.65
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Abiomed (ABMD.O)	E (02/06/2009)	$17.96
Baxter International (BAX.N)	O (09/04/2008)	$69.85
Becton Dickinson (BDX.N)	E (01/03/2013)	$95.84
Boston Scientific (BSX.N)	E (09/10/2010)	$7.35
C.R. Bard (BCR.N)	U (01/03/2013)	$99.15
CareFusion Corp. (CFN.N)	E (01/03/2013)	$34.28
Covidien (COV.N)	O (07/15/2010)	$66.65
Edwards Lifesciences (EW.N)	E (09/04/2008)	$82.81
Grifols (GRFS.O)	O (09/12/2011)	$30
Haemonetics Corporation (HAE.N)	E (05/01/2012)	$39.08
Hansen Medical, Inc. (HNSN.O)	U (01/08/2009)	$1.96
Hill-Rom Holdings Inc. (HRC.N)	E (10/03/2012)	$35.47
Hologic, Inc. (HOLX.O)	O (10/03/2012)	$20.94
Integra LifeSciences (IART.O)	E (09/10/2010)	$33.39
Intuitive Surgical Inc. (ISRG.O)	E (10/02/2007)	$471.07
Johnson & Johnson (JNJ.N)	E (08/10/2010)	$85.45
MAKO Surgical Corp. (MAKO.O)	E (07/11/2011)	$10.34
Medtronic Inc. (MDT.N)	E (09/04/2008)	$46.59
St. Jude Medical (STJ.N)	E (10/29/2012)	$40.97
Stericycle Inc. (SRCL.O)	E (04/06/2011)	$108.54
Stryker Corporation (SYK.N)	O (01/08/2010)	$64.94
Teleflex Inc. (TFX.N)	O (02/11/2013)	$83.7
Zimmer Holdings, Inc. (ZMH.N)	E (07/16/2009)	$74.46

Stock Ratings are subject to change. Please see latest research for each company.
* Historical prices are not split adjusted.

APPENDIX C

Prosthesis Oversizing in Balloon-Expandable Transcatheter Aortic Valve Implantation Is Associated With Contained Rupture of the Aortic Root

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Background—To retrospectively investigate the potential cause of contained rupture of the aortic root in balloon-expandable transcatheter aortic valve implantation (TAVI) by means of pre- and postinterventional multislice computed tomography.

Methods and Results—Seventy-two patients (mean age 82±7 years, mean aortic valve area 0.69±0.19 cm²) underwent balloon-expandable TAVI using the EdwardsSAPIEN Transcatheter Heart Valve (23 mm, n=19; 26 mm, n=50; 29 mm, n=3). Aortic annulus dimensions were quantified by multislice computed tomography–based cross-sectional area assessment and average diameter calculation (CAAD) before and after TAVI. Post-TAVI multislice computed tomography data sets were available in 65 patients; contained aortic root rupture was diagnosed in 3 patients. Pre-TAVI CAAD was 23.1±1.8 mm; post-TAVI CAAD was 22.9±1.3 mm. Median relative change in CAAD pre- and post-TAVI was −0.5% (interquartile range, 3.6%). Relative increase of 5% to 10% was observed in 4 patients (1 with contained rupture), relative increase >10% in 2 patients, both with contained rupture. Mean relative oversizing, calculated as the relative difference in diameter between pre-TAVI CAAD and nominal diameter of the selected prosthesis, was 9.8%±7.8%. Relative oversizing was significantly higher in patients with contained rupture compared with patients without contained rupture (24.6%±5.4% versus 9.1%±6.6%; $P<0.001$). Relative oversizing ≥20% occurred in 6 patients (3 with contained rupture).

Conclusions—Contained rupture of the aortic root in balloon-expandable TAVI is associated with severe prosthesis oversizing. Multislice computed tomography–based assessment of aortic annulus dimension in conjunction with adapted sizing guidelines may reduce the incidence of severe oversizing. **(*Circ Cardiovasc Interv*. 2012;5:540-548.)**

Key Words: TAVI ■ aortic valve stenosis ■ contained rupture ■ pseudoaneurysm ■ computed tomography

Transcatheter aortic valve implantation (TAVI) is increasingly used in patients with severe aortic stenosis who are denied to conventional aortic valve replacement due to severe comorbidities and a perceived high risk of perioperative mortality.[1–4] Preinterventional prosthesis sizing relies on noninvasive imaging modalities such as echocardiography or multislice computed tomography (MSCT).[5] Incorrect sizing may result in adverse outcomes such as paravalvular regurgitation, device embolization,[6,7] or even aortic root rupture in the case of severe oversizing.[8]

Although there is no uniform standard for prosthesis sizing with dissenting results among different image modalities, MSCT is increasingly used because of its capability of 3-dimensional assessment of the complex aortic root anatomy.[9] Recent studies suggest that MSCT might be more suitable to assess the aortic annulus size than 2-dimensional echocardiography.[10–12]

With the introduction of TAVI, performing physicians and surgeons may encounter incidents and complications different from those in conventional aortic valve surgery, such as annulus or aortic root rupture and pseudoaneurysm formation of the aortic root.[8,13–15] These complications may be evident while performing the procedure or may be apparent at follow-up studies. However, data are limited and risk factors for these entities have not been investigated thoroughly yet.

The aim of this study was to investigate the potential cause of contained rupture of the aortic root in balloon-expandable TAVI by means of pre- and postinterventional MSCT and definition of prosthesis oversizing.

Methods

Study Population

This retrospective study was approved by the institutional review board and complies with the Declaration of Helsinki. Between June 2008 and May 2011, 107 patients with severe symptomatic aortic stenosis underwent TAVI, of whom 35 patients received a self-expandable prosthesis and 72 patients a balloon-expandable prosthesis. The study population consisted of the 72 consecutive patients with balloon-expandable TAVI, who underwent either

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WHAT IS KNOWN

- Preinterventional prosthesis-sizing is critical for TAVI in order to reduce the risk of adverse outcomes, such as paravalvular regurgitation or device embolization.
- Three-dimensional imaging modalities, such as multislice computed tomography, are capable of assessing the complex 3-dimensional anatomy of the aortic root complex.

WHAT THE STUDY ADDS

- Follow-up computed tomography after balloon-expandable TAVI can establish the diagnosis of asymptomatic contained aortic root rupture.
- Contained rupture of the aortic root in balloon-expandable TAVI is associated with severe prosthesis oversizing, and was observed in patients with relative oversizing of >20% in relation to the native aortic annulus.
- Multislice computed tomography-based assessment of aortic annulus dimension in conjunction with adapted sizing-guidelines may reduce the incidence of severe oversizing.

transapical (n=59) or transfemoral (n=13) implantation of the Edwards SAPIEN Transcatheter Heart Valve (Edwards Lifesciences LLC, Irvine, CA). All patients were referred for diagnostic workup before TAVI including an electrocardiography-gated dual-source MSCT of the heart as part of their assessment. Transthoracic echocardiography and transesophageal echocardiography (TEE) were performed within a time span of 1 week, usually before MSCT.

Of the 72 patients, 19 patients received a 23-mm prosthesis, 50 received a 26-mm prosthesis, and 3 patients received a 29-mm prosthesis (available since April 2011). The technique of transapical and transfemoral implantation of the Edwards SAPIEN Transcatheter Heart Valve has been described previously.[16,17] Preceding aortic balloon valvuloplasty was performed using a size 20 mm×50 mm balloon (ZMed, NuMed) filled with 1:4 diluted contrast during a brief episode of rapid ventricular pacing. According to the manufacturer's instructions for use, the bioprosthesis was deployed by inflating the balloon with the entire volume in the inflation device.

In the first 31 patients, selection of prosthesis size (23 mm or 26 mm) was a case-to-case decision based on pre- and intraoperative TEE: The 23-mm prosthesis was implanted for annulus sizes ≤21 mm, the 26 mm for annulus sizes between 22 and 24 mm, according to contemporary manufacturers recommendations.[18] In the succeeding 41 patients', prosthesis sizing was based on the calculated average annulus diameter (CAAD) derived from the cross-sectional area (CSA) assessed by means of planimetry in MSCT.[12] For CAAD <22 mm, the 23-mm prosthesis was implanted, and for CAAD of ≥22 to 25 mm the 26-mm prosthesis was implanted. Starting from April 2011, the 29-mm prosthesis was implanted for CAAD ≥25 to 28 mm. Using these cutoff values, relative oversizing with regard to the nominal stent diameter ranges between 4% and 21% for CAAD of 19 to 28 mm. All patients with balloon-expandable TAVI were subject to follow-up MSCT, as routinely performed at our institution.

MSCT Protocol

All computed tomography (CT) examinations were performed using a dual-source CT scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany). For contrast-enhanced data acquisition, 90 to 110 mL of iodinated contrast agent (Imeron 350, Bracco Imaging, Germany) were injected at a flow rate of 4 to 5 mL/s via an 18-gauge needle in an antecubital vein, followed by a 50-mL saline bolus chaser administered at a flow rate of 4 mL/s. The scan was started by means of bolus tracking. Scan parameters for cardiac CT were as follows: reference tube current time product, 360 mAs/rotation; slice acquisition, 2×64×0.6 mm; pitch, 0.2 to 0.43 adapted to heart rate; gantry rotation time, 330 ms; tube voltage 120 kV; CARE Dose4D tube current modulation; scan direction, craniocaudal. For cardiac data acquisition, scan range extended from the carina to the diaphragm as part of a comprehensive scan protocol consisting of an ECG-gated acquisition of the thorax followed by an ungated data acquisition of the abdomen. Follow-up MSCT scan was limited to the cardiac scan range with a reduced amount of contrast media (70 mL) at identical flow rate.

Contraindications for MSCT examination were severely impaired renal function (estimated glomerular filtration rate, <40 mL/min per 1.73 m^2) or previous severe adverse reaction (anaphylactic; ie, profound hypotension, bronchiospasm, severe urticaria) to an iodinated contrast agent. Patients with an estimated glomerular filtration rate between 40 and 60 mL/min per 1.73 m^2 underwent intravenous volume expansion with isotonic crystalloid (1.0–1.5 mL/kg per hour) for 3 to 12 hours before MSCT and for 6 to 24 hours afterward. In addition, these patients received 1200 mg of N-acetylcystein orally twice a day before and after the procedure. Given the clinical characteristics of the study population with severe symptomatic aortic stenosis, no additional β blockade was administered to achieve slower heart rates.

Image Reconstruction

CT data sets were reconstructed at 300 ms past the R-peak (end-systole) with a slice thickness of 0.6 mm and an increment of 0.4 mm using a medium soft tissue convolution kernel B26f and a sharp kernel B46f. All data sets were transferred to a dedicated postprocessing workstation equipped with Aquarius iNtuition (Terarecon Inc, San Mateo, CA).

Dimensions of the aortic annulus were assessed using the concept of a virtual ring joining the basal attachments of all 3 aortic valve cusps, representing the inlet from the left ventricular outflow tract into the aortic root.[19] Using the coronal-oblique and sagittal-oblique views, the corresponding double-oblique transverse view was adjusted to transect through the most caudal attachments of all 3 native cusps, defining the orientation and position of the virtual ring. To assess the CSA, the luminal contours were tracked on the double-oblique transverse plane using automatic vessel analysis with manual correction (Figure 1). Punctiform calcifications at the most basal attachment sites of the cusps were included into the planimetric area when present. CSA and maximum and minimal diameters were noted as displayed by the segmentation software. Using the equation for the area of a circle (πr^2), the average diameter of the encircled area was calculated (CAAD) as follows:

$$\mathrm{CAAD}=2\times\sqrt{\mathrm{CSA}/\pi}$$

Echocardiography

Multiplanar TEE was performed by an experienced cardiologist using a Philips iE33 echocardiography system (Philips Healthcare, Best, The Netherlands). The aortic annulus diameter was assessed on the midesophageal long-axis view (≈120°) of the ascending aorta and aortic valve at end-systole, according to the American Society of Echocardiography guidelines.[20,21] Diameter was defined as the distance between the depicted hinge points of the aortic valve leaflets, using the inner edge-to-inner edge technique, including annulus calcifications.

Post-TAVI MSCT Assessment and Definition of Contained Rupture

Similar to the initial MSCT examinations, we reconstructed coronal-oblique and sagittal-oblique views through the aortic valve prosthesis, with the intersection of both views representing the axis of the unfolded stent. The position of the resulting double-oblique transverse view was adjusted to the ventricular stent ending. CSA was obtained by means of planimetry (Figure 1E–1H). Contained rupture of the aortic root was defined as discernible contrast-filled cavities, that is, pseudoaneurysms, in the immediate vicinity to the aortic root.

Oversizing

For retrospective analysis, CAAD was defined as the standard of reference. Selection oversizing was defined as selection of a 26-mm prosthesis by means of TEE in the setting of a MSCT-based CAAD <22 mm.

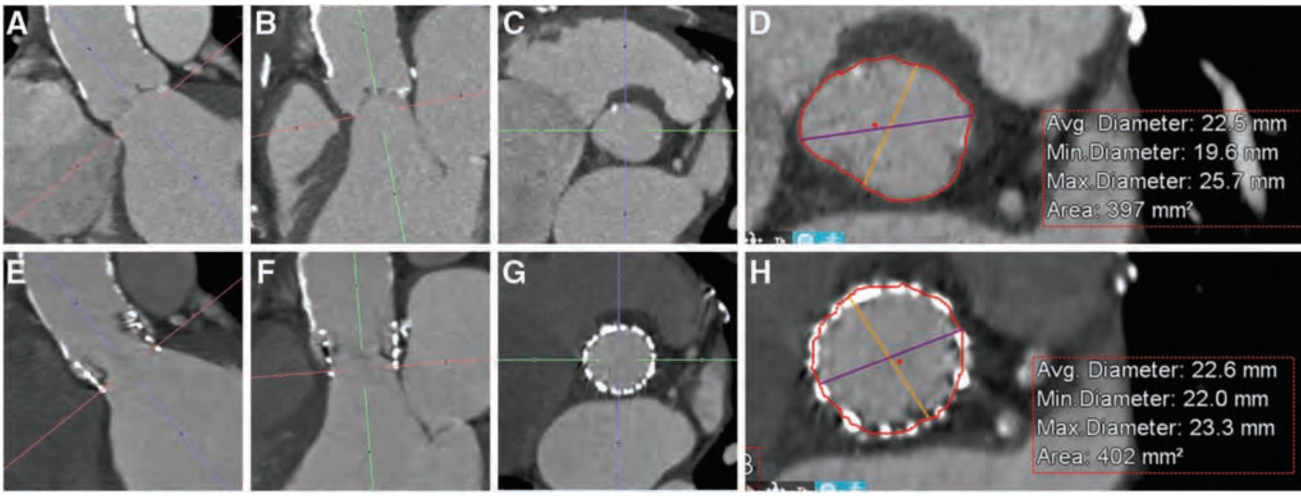

Figure 1. Planimetric assessment of the cross-sectional area of the aortic annulus (**A**–**D**) pre- and (**E**–**H**) post-TAVI. Pre-TAVI: Using the coronal- and sagittal-oblique views, the corresponding double-oblique transverse view was adjusted to transect through the most caudal attachments of all 3 native cusps. Post-TAVI: Analogously to pre-TAVI, the corresponding double-oblique transverse view was adjusted to transect through the ventricular stent ending. TAVI indicates transcatheter aortic valve implantation.

Relative oversizing was calculated as the relative difference in diameter between pre-TAVI CAAD and nominal diameter of the selected prosthesis. Relative change in CAAD between pre-TAVI MSCT and post-TAVI MSCT was calculated.

Statistical Analysis

Continuous variables are reported as means±1 standard deviation when normally distributed as assessed by Kolmogorov–Smirnov tests. Nonnormally distributed variables are reported as the median and interquartile range. Pearson correlation analysis and modified Bland–Altman plots,[22] with the assessment of systematic bias and confidence limits for a single prediction, were used to assess agreement for anatomic measurements by TEE and MSCT. Paired *t* tests were used to test for significant differences between TEE and MSCT measurements. One-way ANOVA was used to test for differences of the eccentricity index (EI) between subgroups. Unpaired *t* test was used to compare relative oversizing between patients with and without contained rupture. All statistical analyses were performed using SPSS software (SPSS 17.0, SPSS Inc, Chicago, IL). A P value <0.05 was considered statistically significant. To quantify the degree of deviation of both, the virtual ring shape and the shape of the cross section of the unfolded stent from a perfect circle, we calculated an EI, where EI = 1−(minimal diameter/maximum diameter).[23] Using this index, an EI of 0 represents a perfect circle, with higher EI indicating elliptical geometry. Noncircular was defined as EI>0.1.

Results

Study Population

Patient characteristics are listed in Table 1. Pre-TAVI MSCT data acquisitions and TEE were successfully performed in all 72 patients. Follow-up MSCT was performed at median 10 days (interquartile range, 12 days) after TAVI. One patient declined follow-up MSCT. Three patients died before follow-up MSCT. Three patients were deferred from follow-up MSCT because of renal failure. Post-TAVI MSCT data sets were thus available in 65 patients. Of them, 18 patients received a 23-mm Edwards SAPIEN valve, 45 patients received a 26-mm valve, and 2 patients received a 29-mm valve. Average heart rate and heart rate variability during data acquisition was 68.3±12.4 bpm and 4.8±6.1 bpm for pre-TAVI data acquisition and 70.5±11.7 bpm and 5.1±6.4 bpm for post-TAVI data acquisition. Average estimated radiation dose for ECG-gated CTA of the entire thorax was 15.4±4.2 mSv.

Procedural Results

Device success (defined as stable device placement and adequate function in the first attempt as assessed by angiography and intraoperative echocardiography) was 100%. Acute procedural success (defined as device success with the absence of periprocedural major cardiovascular events including death, tamponade, and coronary artery occlusion in the first 24 hours after device implantation) was 98.6% (71/72). In-hospital mortality rate was 6.9% (5/72), and 1-month mortality rate was 11.1% (8/72).

Contained Rupture

Signs of contained rupture of the aortic root were observed in 3 of 65 patients (5%). In these patients, contrast-filled cavities were found on follow-up MSCT adjacent to the stent struts with Hounsfield units equivalent to the lumen of the left ventricular outflow tract, not present on initial pre-TAVI MSCT. In all cases,

Table 1. Clinical and Echocardiographic Characteristics of the Study Population

Characteristic	All Patients (n=72)
Age, y*	81.6±6.8
Male/female†	16/56
Body surface area*, m^2	1.78±0.2
Euro score*	21.8±12.5
Echocardiographic findings	
Peak transvalvular aortic gradient*, mm Hg	68.7±21.0
Mean transvalvular aorticgradient*, mm Hg*	41.6±13.5
Aortic valve area*‡, cm^2	0.69±0.19
Ejection fraction*, %	48.6±11.1

*Mean±standard deviations.
†Data are numbers of patients.
‡Aortic valve area as per continuity equation.

Table 2. Annulus Characteristics of Patients With Contained Rupture

Sex, Age, y	Implanted Prosthesis, mm	Sizing	Pre-TAVI TEE, mm	Pre-TAVI CSA/CAAD	Post-TAVI CSA/CAAD	Relative Oversizing, %	Relative Increase in CAAD, %
♀, 77	26	TEE	22	312 mm²/19.9 mm	452 mm²/24.0 mm	30.7	20.6
♀, 84	26	TEE	22	353 mm²/21.2 mm	472 mm²/24.5 mm	22.6	15.6
♀, 89	23	CAAD	19	291 mm²/19.2 mm	346 mm²/21.0 mm	20.4	9.4

CAAD indicates calculated average annulus diameter; CSA, cross-sectional area; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography.

♀ indicates female sex.

the resulting pseudoaneurysm was located adjacent to the left aortic sinus. Annulus and sizing characteristics are listed in Table 2. In all patients, the prosthesis was deployed without technical complications with no abnormal findings on postimplantation intraoperative angiography and intraoperative TEE. There was no postimplantation dilatation in any of the 3 patients.

Two of these patients, both elderly females, had received a 26-mm prosthesis. Both patients were sized by means of TEE (both 22 mm). However, retrospectively performed CAAD assessment revealed diameters of 19.9 mm and 21.2 mm with a relative increase in CAAD of 15.6% and 20.6% post-TAVI (Figure 2). Both patients were discharged on 100 mg aspirin per day. One patient underwent a second follow-up CT 6 months later, which showed the disappearance of the pseudoaneurysm (Figure 3). The other patient (Figure 4) did not undergo a second follow-up CT. She died after being admitted to a community hospital for a traumatic humerus fracture 844 days postimplantation. The cause of death was acute hypoxia most likely related to pulmonary embolism. Autopsy was not performed because of lacking consent by the next of kin.

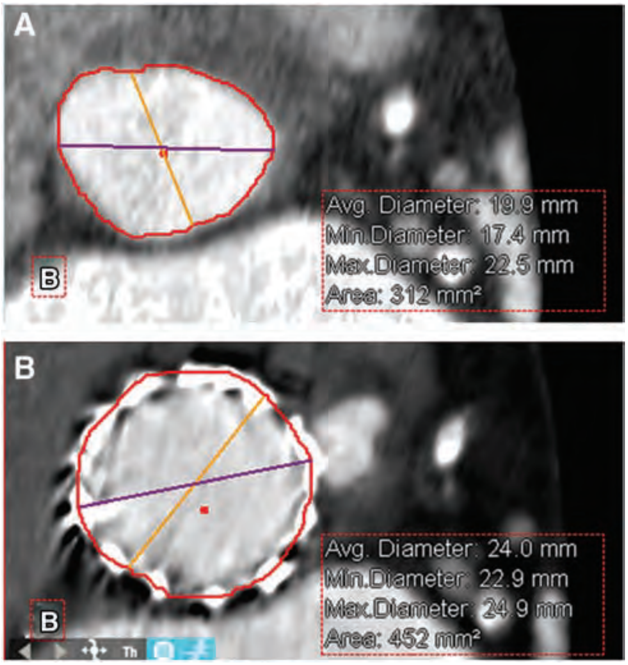

Figure 2. CAAD assessment in a 77-year-old female patient with contained rupture post-TAVI. Pre-TAVI CAAD was 19.9 mm (**A**) and post-TAVI CAAD was 24.0 mm (**B**), resulting in a relative increase in CAAD of 20.6%. CAAD indicates calculated average annulus diameter; TAVI, transcatheter aortic valve implantation.

The third patient, also an elderly female, was sized by means of CAAD and had received a 23-mm prosthesis, given a CAAD of 19.2 mm. Relative increase in CAAD was 9.4%. She died 15 days postimplantation because of respiratory failure after sustained retroperitoneal hematoma and prolonged intubation.

Among the 72 patients treated with balloon-expandable TAVI, there was 1 documented case of acute cardiac tamponade, which was due to insufficiency of the apical myocardial suture. There were no other unresolved cases of acute or subacute cardiac tamponade.

Aortic Annulus Dimensions

The median CSA at the level of the basal attachments of all 3 aortic valve cusps was 420.9 mm² (range, 301–564 mm²); the corresponding mean CAAD was 23.1±1.8 mm (19.6–26.8 mm). Mean minimal diameter was 20.2±2.3 mm (15.8–26.2 mm) and mean maximal diameter 26.3±1.9 mm (21.6–30.0 mm).

TEE Versus MSCT

Mean annulus diameter as assessed with TEE was 21.9±1.7 mm and significantly lower than mean CAAD (23.1±1.8 mm; $P<0.001$). Mean difference between CAAD measurements on MSCT and midesophageal long-axis view on TEE was 1.2±1.7 mm (range −3.1 to 4.6 mm). Limits of agreement according to Bland–Altman analysis were −2.2 mm and 4.6 mm (Figure 5).

Post-TAVI Dimensions and Relative Change in CAAD

The stent's mean CSA was 413.6±47.7 mm² (range, 302–546 mm²); the corresponding mean CAAD 22.9±1.3 mm (range, 19.6–26.4 mm). The stent's CSA was close to a perfect circle (EI<0.1) in 43 patients (66%) and elliptical in the other 22 (34%). Mean EI was 0.10±0.04. None of the prostheses unfolded to its nominal diameter.

Overall, median relative change in CAAD between pre-TAVI and post-TAVI was −0.5% (interquartile range, 3.6%; range −10.4% to 20.6%). Figure 6A depicts the distribution of relative change in CAAD. A relative increase of 5% to 10% was observed in 4 patients, of whom 1 patient demonstrated signs of contained rupture of the aortic root. A relative increase of >10% was found in 2 patients, both with contained rupture.

Valve Selection and Oversizing

In the first 31 patients, prosthesis choice was TEE based: 11 patients had received a 23-mm prosthesis and 20 patients had received a 26-mm prosthesis. Retrospective comparison

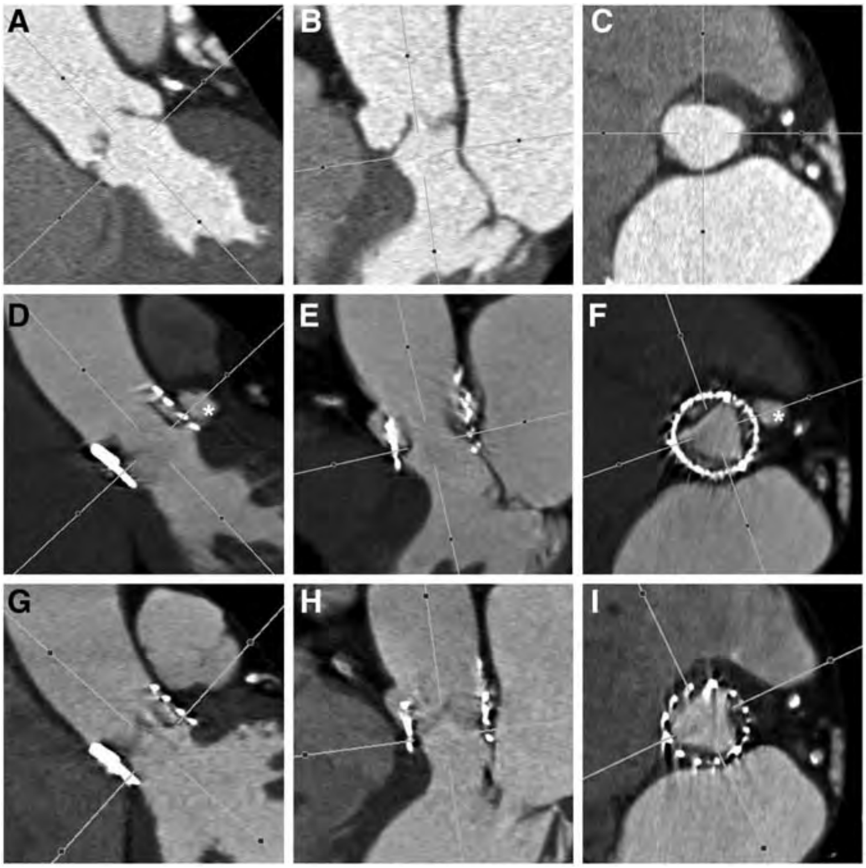

Figure 3. A 77-year-old female patient with aortic stenosis (**A–C**) pre-TAVI multislice computed tomography) and contained rupture (*) status post-TAVI (**D–F**) and spontaneous remission on further follow-up CT (**G–I**). The first column depicts the coronal-oblique views, the second column represents the sagittal-oblique views, and the third double-oblique transverse views. TAVI indicates transcatheter aortic valve implantation.

of implanted prosthesis size (23 or 26 mm) with preoperative CAAD measurements revealed that selection oversizing had occurred in 5 of the 20 patients with a 26-mm prosthesis (CAAD<22 mm). All these patients had follow-up MSCT available, and in 2 patients, contained rupture was diagnosed (relative increase in CAAD 15.6% and 20.6%). The other 3 patients with selection oversizing showed a relative increase in CAAD between 6.4% and 7.4% without the evidence of contained rupture.

Average change of CAAD in patients with contained rupture, in patients with selection oversizing but no rupture, and in patient without selection oversizing was 15.2%±5.6%, 7.0%±0.5%, and −1.6%±3.4%, respectively (P<0.001).

Distribution of relative oversizing by comparison of nominal stent diameter and CAAD is depicted in Figure 6B. Mean relative oversizing was 9.8%±7.3% (range −4.6% to 30.7%). Relative oversizing ≥10% occurred in 27 patients. Relative oversizing ≥20% occurred in 6 patients, of whom 3 showed evidence of contained rupture. Oversizing was significantly higher in patients with contained rupture compared to patients without contained rupture (24.6±5.4% versus 9.1%±6.6%; P<0.001).

Eccentricity

The mean calculated EI was 0.23±0.09 (range, 0.11–0.40). The annulus shape was elliptical (EI>0.1) in all patients. Average EI in patients with contained rupture, in patients with selection oversizing but no rupture, and in patients without selection oversizing was 0.24±0.10, 0.25±0.13, and 0.24±0.07 (P=0.944), respectively.

Paravalvular Regurgitation

Moderate, but not severe, paravalvular regurgitation was observed in 3 patients immediately after the intervention by intraoperative TEE and by TTE at time of discharge. There was no paravalvular regurgitation in the 3 patients with contained rupture and in the 3 remaining patients with selection oversizing but without contained rupture.

Discussion

With TAVI, the occurrence of uncontained and contained aortic annulus rupture, the latter also referred to as pseudoaneurysm formation of the left ventricular outflow tract, has been described previously.[8,13,15,24] In theory, both entities may belong to the spectrum of the same pathology, namely disruption of the aortoventricular junction, caused by either the forces of the preceding valvuloplasty or the actual TAVI procedure. In the study presented, we found 3 cases of contained rupture of the aortic root by means of MSCT. Contained rupture occurred only in patients with pronounced increase in CAAD between pre-TAVI and post-TAVI MSCT data sets and relative oversizing >20%.

The balloon-expandable Edwards SAPIEN Heart Valve is available with 23 mm and 26 mm in size, and since recently with 29 mm. Current manufacturer's recommendations for valve sizing are TEE based. Furthermore, in the majority of recent single- and multicenter studies, valve size selection is based on measurements by TEE. As described by Walther et al,[18] patients with an aortic annulus diameter <21 mm receive a 23-mm prosthesis whereas patients with an aortic anulus

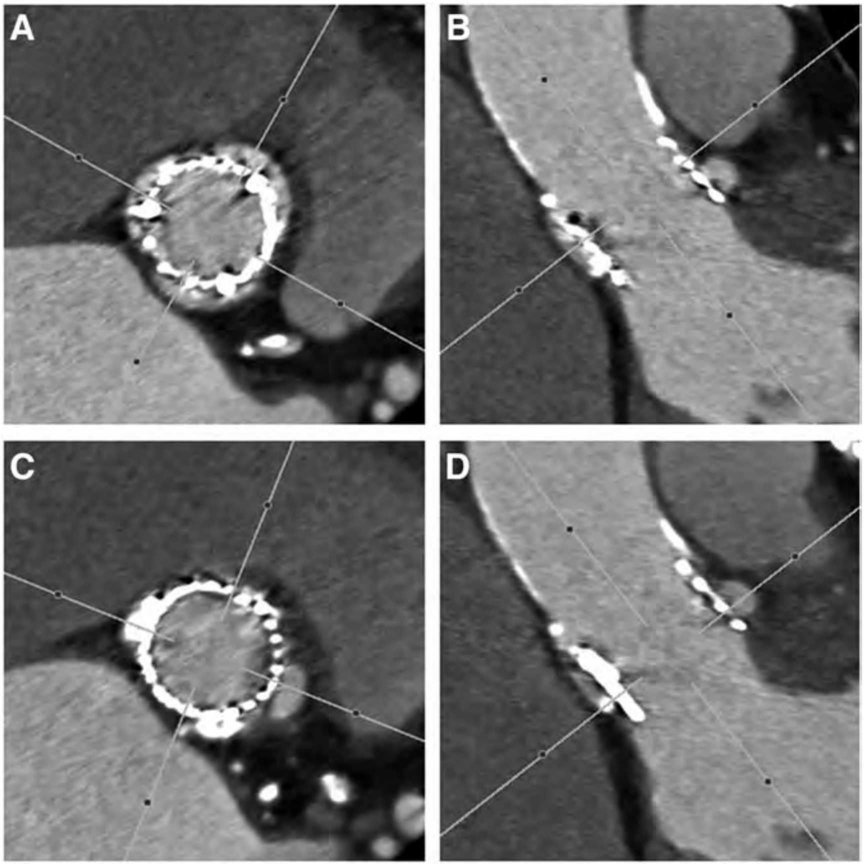

Figure 4. An 84-year-old female patient with status post-TAVI and contained rupture on follow-up multislice computed tomography in close anatomic relation to the left aortic sinus. **A**, the double-oblique transverse view at the level of the native aortic sinus, (**B**) the coronal-oblique view through the aortic root (red line indicates level of **A**), (**C**) the double-oblique transverse view at the level of the pseudoaneuryms, (**D**) coronal-oblique view through the aortic root (red line indicates level of **C**). Relative increase in calculated average annulus diameter was 15.6%. TAVI indicates transcatheter aortic valve implantation.

diameter between 22 and 24 mm receive a 26-mm prosthesis. In their opinion, some oversizing of ≈10% is essential to avoid severe paravalvular leakage, but in the presence of a rigid aortic root, too much oversizing should be avoided.[18] However, according to Webb et al[17], an annulus diameter of 18 to 22 mm assessed by echocardiography is considered appropriate for the 23-mm prosthesis and 21 to 25 mm for the 26-mm prosthesis, creating a twilight zone between 21 and 22 mm.

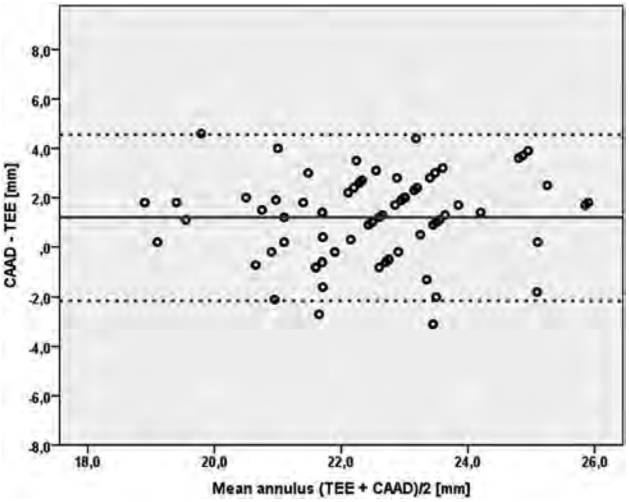

Figure 5. TEE vs MSCT annulus assessment (n=72): Bland-Altman plot of pre-TAVI TEE measurements and pre-TAVI MSCT calculated average annulus diameter (CAAD)measurements. The mean difference of measurements was 1.2±1.7 mm, indicating that TEE underestimates the average annulus diameter. MSCT indicates multislice computed tomography; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography.

Unfortunately, the aortic annulus is not a true ring. The semilunar hinges of the aortic leaflets take the form of a 3-pronged coronet rather than a circle.[19] Furthermore, the annulus is rather elliptical than round when viewed axially.[12,25] Given this complex and ovoid geometry, different imaging modalities as well as measurement planes will yield dissenting results. We found that 2-dimensional-TEE systematically underestimated annulus dimensions by 1.2±1.7 mm when compared with CAAD. This can be partially attributed to the ovoid annulus anatomy and the midesophageal long-axis view orientation, transecting through the right and noncoronary cusps, more closely resembling the short annulus axis.[12,25] Furthermore, limits of agreement were rather wide with patients having smaller but, importantly, also larger diameters in TEE than in CT. Larger intraindividual diameters in TEE than in MSCT may be due to the varying diameter of the aortic root, which is widest at the midpoints of the sinuses and smaller at the basal attachment of the leaflets. The leaflets' hinges extend from the basal attachment to the sinotubular junction, following the varying root caliber. With TEE, hinge-to-hinge measurements from the basal attachment of 1 leaflet to the depicted hinge point across the lumen may take a diagonal path in relation to the aortic root's axis, thus yielding a larger value, further augmented by the aortic root's wider diameter toward the midpoint of the sinuses.

In contrast to the elliptical annulus anatomy, devices for balloon-expandable TAVI are circular when viewed axially.

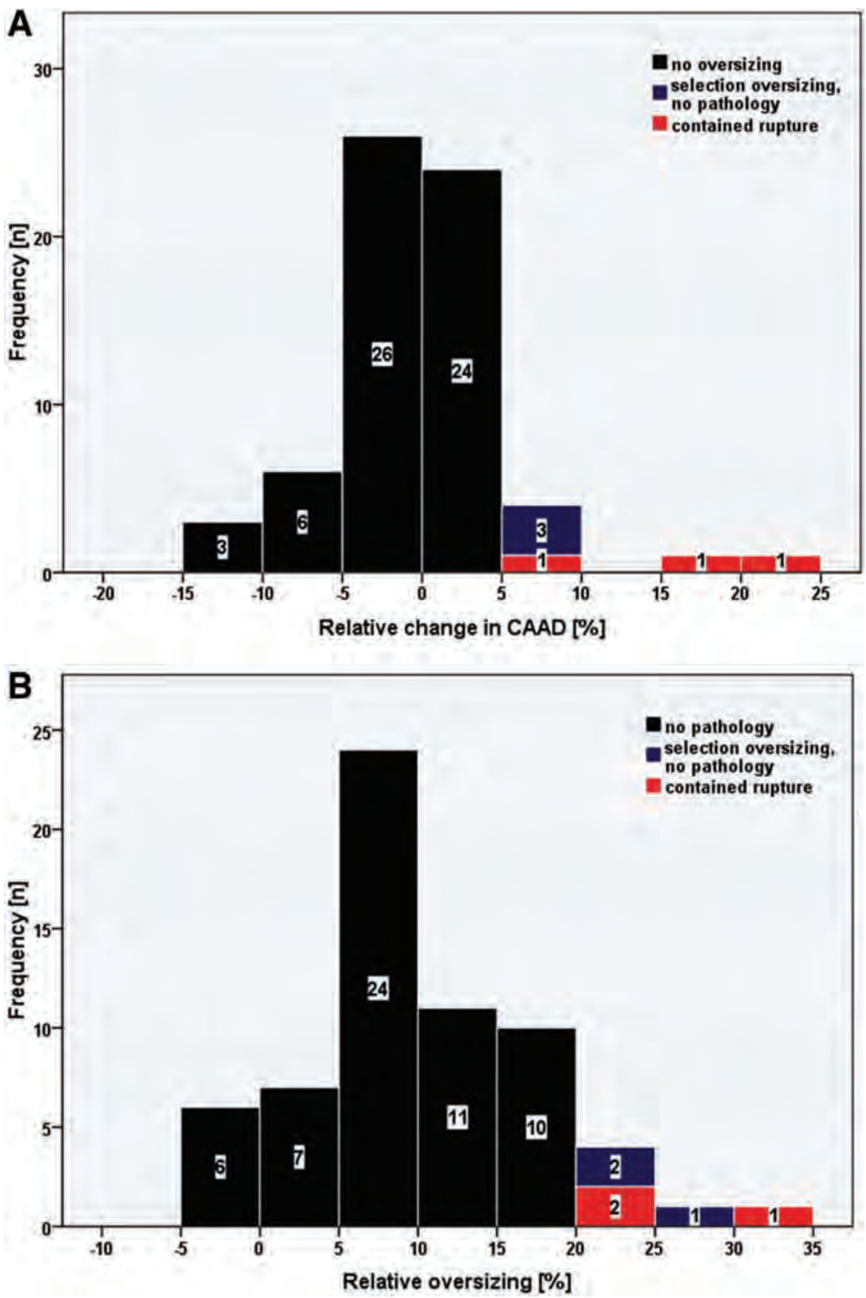

Figure 6. Distribution of relative change in CAAD between pre-TAVI and post-TAVI data sets (**A**) and distribution of relative oversizing by comparison of nominal stent diameter and CAAD (**B**). Histogram intervals are 5%, n=65. CAAD indicates calculated average annulus diameter; TAVI, transcatheter aortic valve implantation.

As recently demonstrated, the Edwards SAPIEN Transcatheter Heart Valve expands to an almost circular shape in most patients,[12,25] thereby altering the annulus configuration, that is, reducing eccentricity toward a more circular shape while the CSA remains constant.[12,26] In the study presented, the median relative change in CAAD was −0.5% when comparing pre- and post-TAVI data sets. An increase of ≥5% was observed in only 6 of 65 patients, and an increase of >10% in only 2 patients. Although increase in CAAD was significantly higher in patients with contained rupture, contained rupture was not observed in patients with only moderate increase in CAAD.

Furthermore, relative oversizing, expressing the mismatch of CAAD and nominal prosthesis diameter, was significantly higher in patients with contained rupture. Contained rupture was only found in patients with relative oversizing >20%. We identified 2 reasons for pronounced relative oversizing: (1) selection oversizing by choosing a larger prosthesis because of borderline TEE measurements; and (2) small annulus anatomy by choosing the smallest prosthesis currently available.

Given the systematic difference in annulus dimensions obtained by TEE and MSCT, TEE-based sizing guidelines cannot be simply adopted to MSCT. Considering the ovoid nature of the annulus and the circular nature of the ideally unfolded Edwards SAPIEN prosthesis, it becomes apparent that the recommended TEE-based oversizing by 10% as stated by Walther et al[18] does not necessarily imply oversizing in terms of CAAD. Instead, the recommended oversizing by 10% compensates for the intrinsic bias of the midesophageal long-axis view on TEE, yielding smaller values than the CAAD. For the CAAD-based sizing approach, which is now routinely applied at our institution, we deliberately chose 22 mm as the cutoff value for selection between the 23-mm

and the 26-mm prosthesis as we learned that neither of both unfolds to the nominal diameter. Since recently, the 29-mm prosthesis is chosen for CAAD of 25 to 28 mm. However, given the results of this study, it is unclear how to treat patients with a small annulus (eg, <20 mm).

Despite >30 000 TAVI procedures performed worldwide, literature on pseudoaneurysm formation and contained rupture is limited to case reports, as follow-up MSCT is not routinely performed. However, uncontained annulus rupture with cardiac tamponade and fatal outcome has been observed in larger studies. Thus, pseudoaneurym formation might represent the lower end of the spectrum of manifestations with uncontained rupture and cardiac tamponade on the upper end. In fact, in real world single-center (eg, Pasic et al,[8] 1 of 194 patients; Lange et al,[24] and 1 of 129 patients) or multicenter registries (Eltchaninoff et al,[27] 1 of 95 patients), the rate of uncontained aortic annulus rupture ranges between 0.5 % and ≈1%.

As patients included into this study underwent TAVI as they did not qualify for open surgery in the first place due to a perceived high risk of perioperative mortality, the 3 patients with contained rupture underwent conservative management only. Although the clinical impact of untreated contained rupture is unknown, it appears conceivable that the occurrence of contained rupture as an assumed prestage to uncontained rupture should be avoided. Interestingly, in all 3 cases observed in the present study, as well as in the 2 cases described in literature so far,[13,15] contained rupture occurred adjacent to the left coronary sinus. This leads to the assumption that the tissue adjacent to the left coronary sinus represents a Locus minoris resistentiae. Furthermore, all 3 patients were elderly women, concordant with observations by others.[24]

Study Limitations

This study is limited by its relatively small patient cohort and the rare incidence of pseudoaneurysm formation. However, as to our knowledge, this is the largest patient series with systematic follow-up MSCT to date. Furthermore, the time span from TAVI to follow-up varied between 3 and 66 days. Thus, smaller alterations might have been missed in some patients, as pseudoaneurysm may regress with time. Finally, because this study focused on patients with balloon-expandable TAVI, the presented concept cannot be readily applied for self-expanding devices.

Optimal sizing can be thought of being in-between excessive oversizing with subsequent rupture and undersizing with subsequent paravalvular regurgitation. Our MSCT-based sizing regiment results in relative oversizing of 4% to 21% for CAAD of 19 to 28 mm using the 3 currently available prosthesis sizes of 23, 26, and 29 mm (Europe). However, our retrospective study was not designed to investigate the optimal amount of oversizing.

Planimetry is one of the few different measurement techniques for the assessment of annulus dimensions with MSCT. Others are caliper measurements. However, planimetry followed by calculation of an average diameter has been shown to be the most reproducible measurement among different measurement techniques with MSCT.[28] Importantly, data reconstruction was deliberately chosen at 300 ms past the R-peak to ensure proper image quality, even in patients with atrial fibrillation.

Conclusion

Contained rupture of the aortic root in balloon-expandable TAVI is associated with severe prosthesis oversizing. MSCT-based assessment of aortic annulus dimension in conjunction with adapted sizing guidelines may reduce the incidence of prosthesis oversizing.

Disclosures

None.

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APPENDIX D

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CLINICAL STUDIES

Coronary Obstruction After Transcatheter Aortic Valve Implantation

A Systematic Review

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Objectives This study sought to evaluate, through a systematic review of the published data, the main baseline characteristics, management, and clinical outcomes of patients suffering coronary obstruction as a complication of transcatheter aortic valve implantation (TAVI).

Background Very few data exist on coronary obstruction after TAVI.

Methods Studies published between 2002 and 2012, with regard to coronary obstruction as a complication of TAVI, were identified with a systematic electronic search. Only the studies reporting data on the main baseline and procedural characteristics, management of the complication, and clinical outcomes were analyzed.

Results A total of 18 publications describing 24 patients were identified. Most (83%) patients were women, with a mean age of 83 ± 7 years and a mean logistic European System for Cardiac Operative Risk Evaluation score of 25.1 ± 12%. Mean left coronary artery (LCA) ostium height and aortic root width were 10.3 ± 1.6 mm and 27.8 ± 2.8 mm, respectively. Most patients (88%) had received a balloon-expandable valve, and coronary obstruction occurred more frequently in the LCA (88%). Percutaneous coronary intervention was attempted in 23 cases (95.8%) and was successful in all but 2 patients (91.3%). At 30-day follow-up, there were no cases of stent thrombosis or repeat revascularization, and the mortality rate was 8.3%.

Conclusions Reported cases of coronary obstruction after TAVI occurred more frequently in women, in patients receiving a balloon-expandable valve, and the LCA was the most commonly involved artery. Percutaneous coronary intervention was a feasible and successful treatment in most cases. Continuous efforts should be made to identify the factors associated with this life-threatening complication to implement the appropriate measures for its prevention. (J Am Coll Cardiol Intv 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation

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Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement in those patients considered at very high or prohibitive risk for surgery (1). Despite its more widespread adoption as a treatment option and the increasing experience of the centers, TAVI is still associated with complications, such as vascular/bleeding and cerebrovascular events, conduction abnormalities requiring permanent pacemaker implantation, and significant residual aortic regurgitation (1). The relatively high rate of such complications has made possible an accurate evaluation of their predictive factors and clinical consequences, and this does indeed represent a first step in the way of implementing appropriate preventive measures and treatment. Nonetheless, TAVI has also been associated with very rare but life-threatening complications, such as coronary ostia obstruction. Specific clinical data on this important complication—apart from some reports on its incidence (usually <1%) in some TAVI series (2–8)—have been scarce and restricted to case reports and small case series, precluding any appropriate evaluation of the baseline characteristics of patients suffering this complication as well as its management and clinical impact. The objective of the present study was to provide further insight into the baseline characteristics, management, and clinical outcomes of patients with coronary obstruction as a complication of TAVI through a systematic review of all the studies on TAVI and coronary obstruction published thus far.

Abbreviations and Acronyms

CABG = coronary artery bypass graft

CAD = coronary artery disease

CT = computed tomography

LCA = left coronary artery

PCI = percutaneous coronary intervention

TAVI = transcatheter aortic valve implantation

Methods

All relevant papers published in English about TAVI and coronary obstruction published between December 2002 and July 2012 were systematically searched in BioMedCentral, Google Scholar, and PubMed. The following query terms were used: aortic stenosis, transcatheter aortic valve implantation, transcatheter aortic valve replacement, transcatheter heart valve, heart valve prosthesis implantation, coronary stenosis, coronary occlusion, and coronary obstruction. Further studies were sought by means of a manual search of secondary sources, including references from primary papers (backward snowballing) and contacts with international experts.

Citations were first screened at the title/abstract level by 2 independent reviewers (HBR, LNF) and retrieved as complete manuscripts if potentially pertinent. Divergences were resolved after consensus, to gather all the pertinent case reports and case series concerning coronary obstruction in TAVI. Published papers that included only the incidence of the complication without any case description were excluded from this analysis.

Gathered data included baseline clinical, echocardiographic, and computed tomography (CT) characteristics. The CT variables included data on left coronary artery (LCA) ostium height from aortic annulus, severity and distribution of valve calcification, and aortic root and annulus diameters. Procedural data on the type and size of the transcatheter valve, approach, and clinical presentation and management of coronary obstruction were recorded. Finally, data on in-hospital or 30-day mortality and clinical status at follow-up, including the need for repeat revascularization, were also gathered.

Categorical variables were reported as n (%), and continuous variables were reported as mean ± SD. Group comparisons were performed with the chi-square test for categorical variables and Student *t* test adjusted for multiple comparisons (Bonferroni method) for continuous variables. The results were considered significant with p values <0.05. All analyses were conducted with the statistical package SAS (version 9.3, SAS Institute, Inc., Cary, North Carolina).

Results

Between January 2002 and May 2012, 19 publications describing a total of 27 patients who had experienced coronary obstruction related to a TAVI procedure were identified (9–27). All studies referred to single case reports or small series, with a maximum of 5 reported cases of coronary obstruction. Three cases with previous surgical aortic valve prosthesis ("valve-in-valve" procedure) were excluded from this analysis (24,27), leading to a final study population of 24 patients. The main baseline clinical characteristics were available in all patients. The CT data on left main ostium height and annulus and aortic root measurements were reported in 13, 12, and 8 patients, respectively. No data were reported on the severity and distribution of valve calcification. Procedural and clinical data on the clinical presentation, diagnosis, and management of the coronary obstruction were available in all patients. All studies reported data on in-hospital outcomes, 12 studies (including 16 patients) reported data on 30-day outcomes, and 11 studies (including 14 patients) reported data at follow-up.

The main clinical, echocardiographic, CT, and procedural characteristics of the patients are shown in Tables 1 (individual data) and 2 (mean data). Mean age of the study population was 83 ± 7 years, and most patients were women (83.3%). The main baseline characteristics of the study population compared with those reported in the largest TAVI registries (3,4,6–8,28–31) (pooled data) and the PARTNER (Placement of Aortic Transcatheter Valve) trial (5,32) are shown in Figure 1. The CT data revealed a mean LCA ostia height of 10.3 ± 1.6 mm and aortic root width of 27.8 ± 2.8 mm. The mean values of LCA height

Table 1. Individual Data on Baseline Clinical and Procedural Characteristics

Patient	Age	Sex	Previous CABG	Logistic EuroSCORE (%)	Mean Aortic Gradient (mm Hg)	Aortic Annulus (mm)	Aortic Root (mm)	LCA Height (mm)	Approach	Valve Type	Valve (mm)
1 (9)	85	F	No	13.3	88	22.0	—	9.1	TA	SAPIEN	26
2 (10)	87	—	No	—	—	—	—	—	TF	SAPIEN	—
3 (11)	85	F	No	18.0	45	—	—	—	TF	SAPIEN	23
4 (12)	81	F	No	21.0	—	—	—	>12	TA	SAPIEN	26
5 (12)	85	F	No	23.8	—	—	—	>12	TF	SAPIEN XT	23
6 (12)	80	M	No	31.0	—	—	—	>12	TA	SAPIEN XT	29
7 (13)	86	F	No	24.3	51	22.4	31.3	9.7	TF	SAPIEN	26
8 (13)	78	F	Yes	51.5	46	19.3	27.8	10.3	TA	SAPIEN	23
9 (13)	80	F	No	25.3	58	20.9	26.4	9.0	TA	SAPIEN	23
10 (13)	88	F	No	22.0	55	18.0	26.2	11.0	TA	SAPIEN	23
11 (13)	82	M	No	20.7	43	22.1	33.0	9.0	TA	SAPIEN	23
12 (14)	86	M	No	—	—	—	—	—	TF	SAPIEN	23
13 (15)	87	F	No	—	60	20.0	—	—	TF	SAPIEN	23
14 (16)	87	F	No	—	70	20.0	—	—	TA	SAPIEN	23
15 (17)	58	F	No	—	57	—	—	—	TF	SAPIEN	26
16 (18)	86	F	No	—	—	—	—	—	TF	SAPIEN	23
17 (19)	82	F	No	—	—	—	—	7.0	TF	SAPIEN	23
18 (20)	68	F	No	8.8	46	21.6	26.4	—	TA	SAPIEN	26
19 (21)	86	F	No	31.2	55	—	—	10.2	TF	SAPIEN	23
20 (22)	76	F	No	9.1	90	24.0	—	—	TF	SAPIEN XT	26
21 (23)	86	F	No	—	68	—	—	—	TF	SAPIEN XT	23
22 (24)	86	F	No	45.0	—	20.0	27.0	11.0	TF	CoreValve	26
23 (25)	89	F	No	25.3	65	20.0	—	12.0	TF	CoreValve	26
24 (26)	87	M	No	—	—	—	—	—	TF	CoreValve	29

SAPEIN and CoreValve (Medtronic, Minneapolis, Minnesota).
CABG = coronary artery bypass graft; CAD = previous coronary artery disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; F = female; LCA = left coronary artery; M = male; TA = transapical; TF = transfemoral.

and aortic root diameter compared with the values obtained in a previous population of patients with and without aortic stenosis (33,34) as well as that of patients referred for TAVI (35) are shown in Figure 2. A balloon-expandable Edwards valve (Edwards Lifesciences, Irvine, California) was used in most (87.5%) cases.

The main data on clinical presentation and management of coronary obstruction are shown in Tables 3 (individual data) and 4 (mean data). Most (87.5%) cases presented with persistent severe hypotension. Onset of symptoms occurred immediately after valve implantation in 20 patients (83.3%), within the first few hours after the procedure in 2 patients (8.3%), and within the first 2 days after the procedure in another 2 patients (8.3%). Coronary obstruction occurred more frequently in the LCA (83.3%), and the diagnosis was made by coronary angiography in all patients but 1 (post-mortem). Coronary obstruction was related to the displacement of a calcified native aortic valve leaflet toward the coronary ostium in all patients, except for 1 patient with aortic valve cusp shearing and migration into the LCA.

Percutaneous coronary intervention (PCI) was attempted in 23 patients (95.8%) and was successful in all but 2 (91.3%). At least 1 stent was implanted at the coronary ostia in 20 patients. Significant compression of the stent requiring the implantation of a second stent occurred in 3 patients, whereas conversion to open heart surgery was required in 2 patients. The 2 unsuccessful PCI cases consisted of a failure to cross the obstruction with the coronary wire, requiring emergency coronary artery bypass graft (CABG), and a failure to re-establish coronary flow despite successful stent implantation, leading to continuous cardiogenic shock and death.

Hospital mortality rate was 8.3%, and all patients who had successful PCI survived and were discharged from the hospital at a mean of 7 ± 4 days after the intervention, with no cases of stent thrombosis or repeat revascularization. Data at follow-up (mean of 10 ± 6 months) were available in 14 patients, and all of them were alive and in New York Heart Association functional class I or II at that time. One patient needed repeat revascularization due to stent restenosis at 4-month follow-up.

Discussion

The main findings of this systematic review of the published data on symptomatic coronary obstruction after TAVI

Table 2. Baseline Clinical, Echocardiographic, CT, and Procedural Characteristics of the Study Population

Clinical Variables	
Age, yrs	82.5 ± 7.0
Female	20 (83.3%)
NYHA	
I–II	18.2%
III–IV	81.8%
Previous CABG	1 (4.2%)
Logistic EuroSCORE (%)	25.1 ± 12.0
Echocardiographic and CT Data	
Mean aortic gradient, mm Hg	59.8 ± 14.5
Indexed aortic valve area, cm^2/m^2	0.43 ± 0.09
Aortic annulus, mm	20.8 ± 1.6
Left main height, mm	10.3 ± 1.6
Aortic root width, mm	27.8 ± 2.8
Procedural data	
Approach	
TF	15 (62.5%)
TA	9 (37.5%)
Valve type	
SAPIEN and SAPIEN XT	21 (87.5%)
23 mm	13 (54.2%)
26 mm	6 (25.0%)
29 mm	1 (4.2%)
Unknown	1 (4.2%)
CoreValve	3 (12.5%)
26 mm	2 (8.3%)
29 mm	1 (4.2%)
Ratio valve/annulus	1.19 ± 0.07

N = 24.
NYHA = New York Heart Association functional classification; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

showed that this complication occurred more frequently in women and in patients with no prior CABG. In these cases, the mean height of the LCA ostium was approximately 10 mm (range 7 to >12 mm), and the mean diameter of the aortic root was approximately 28 mm (range 26 to 33 mm). Also, the vast majority of reported cases of coronary obstruction post-TAVI occurred in patients who had received a balloon-expandable valve. Clinical presentation included: persistent severe hypotension, ST-segment changes, and ventricular arrhythmias, all of which occurred immediately after valve implantation in most cases. An LCA ostia obstruction was more frequent than RCA obstruction, and most patients were treated with PCI, which was successful in approximately 90% of them. However, conversion to open heart surgery and mechanical hemodynamic support were required in approximately 8% and 25% of PCI attempts, respectively. Importantly, significant compression of the implanted stent was observed in 13% of the cases, requiring the implantation of a second stent in all of them. There were no cases of acute stent thrombosis or repeat revascularization, and the in-hospital mortality rate for the entire study population was 8.3% (0% in those patients with a successful PCI).

Coronary obstruction after TAVI was first described in the first TAVI experimental porcine model (36), and this potential complication was subsequently confirmed by other authors in different experimental models (37). The occurrence of coronary obstruction after TAVI in humans was first described in 2006 (10), and its reported incidence has usually been <1%, ranging from 0% to 4.1% in contemporary series (10,13,38–40). The rates of coronary obstruction in recent TAVI registries and in the PARTNER trial are summarized in Table 5.

Factors associated with coronary obstruction after TAVI. The most frequent mechanism associated with coronary obstruction after TAVI has been the displacement of the calcified native cusp over the coronary ostium, and this has also been confirmed by the present review of the published data. In fact, no cases of coronary obstruction related to the struts of the transcatheter valve frame or to the cuff/leaflets of the transcatheter valve itself have been reported to date. Although the final mechanism leading to coronary obstruction after TAVI is well understood, the risk factors that predispose a patient to its occurrence remain largely unknown. A low position of the coronary ostia with respect to the aortic annulus has been highlighted as one of the most important factors contributing to this complication, and it has been suggested that a coronary ostia height cutoff ≤10 mm increases the risk of coronary obstruction during TAVI (41,42). In a recent post-mortem study, including 51 normal hearts, the mean LCA height, as determined by the LCA distance to the bottom of the corresponding sinus, was 12.6 ± 2.6 mm (43). In another study that evaluated the aortic root with multislice CT in 169 patients with and without aortic stenosis, the mean distance from the basal attachment point of the aortic valve leaflets to the ostium of the LCA was 14.4 ± 2.9 mm, with no differences between patients with and without aortic stenosis (34). Akhtar et al. (33) found that aortic stenosis was associated with a shorter distance from the aortic valve annulus to the LCA ostium (13.4 ± 3.2 mm vs. 15.6 ± 2.7 mm; $p = 0.01$). The present study showed that the mean height of the LCA ostium in the reported cases of coronary obstruction after TAVI was 10.3 mm (range 7 to >12 mm), a mean value that seems to be significantly lower (2 to 5 mm) compared with that reported in prior pathological and CT studies in patients with and without aortic stenosis (Fig. 2). However, this mean coronary ostium height value was higher than the previously suggested 10-mm "safety" cutoff, and indeed, approximately 60% of the cases with coronary obstruction after TAVI had a coronary ostia height >10 mm. This suggests that factors other than a short-distance between the aortic annulus and coronary ostia might also be involved in the occurrence of this complication.

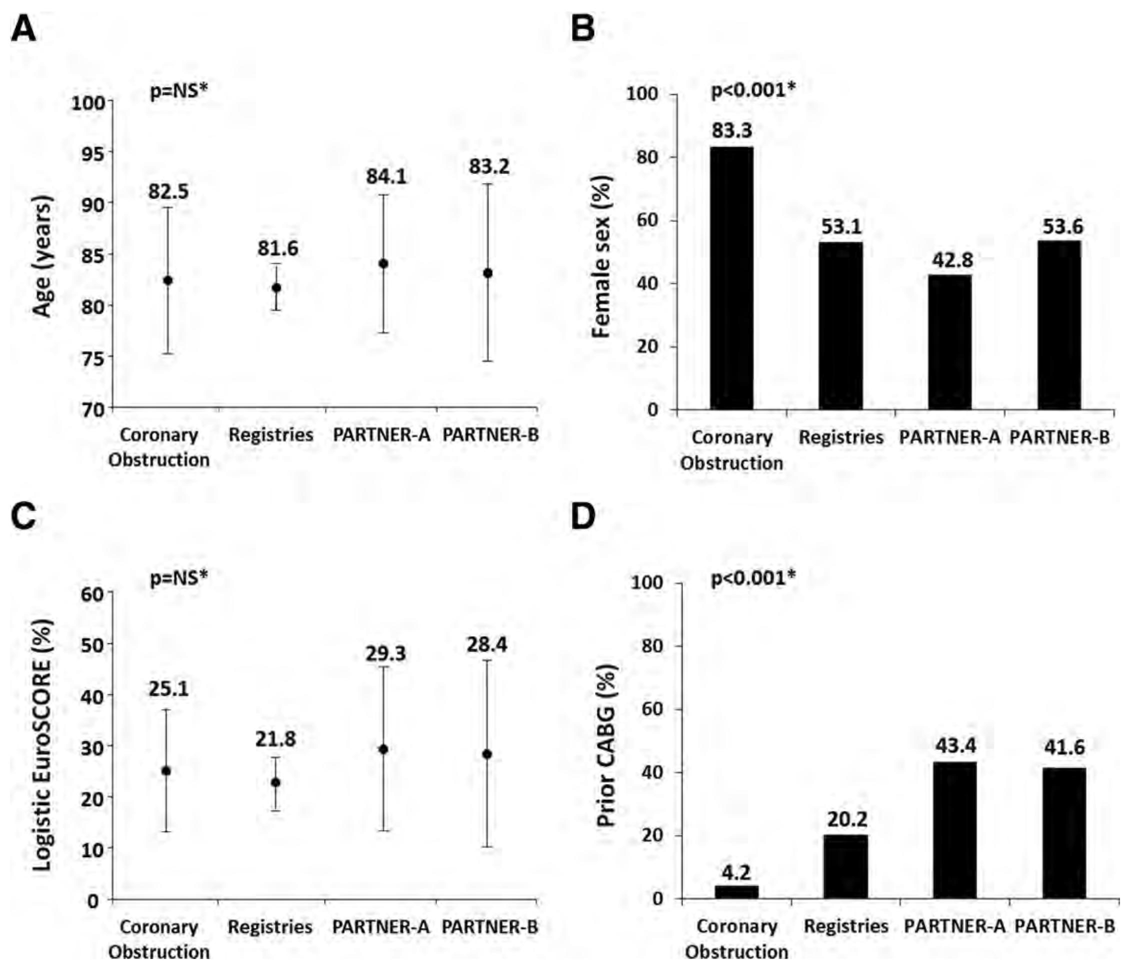

Figure 1. Main Baseline Clinical Characteristics

Main baseline characteristics of the study population compared with the largest transcatheter aortic valve implantation registries (3,4,6–8,28–31) (pooled data) and the PARTNER (Placement of Aortic Transcatheter Valve) trials (5,32), including mean age **(A)**, female sex **(B)**, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) **(C)**, and prior coronary artery bypass graft (CABG) **(D)**. *Coronary obstruction versus other groups.

The severity of valve calcification and, especially, the presence of bulky calcium nodules on the left or right aortic leaflets have also been suggested as important predictive factors for coronary obstruction after TAVI. However, the degree of valve calcification or the presence of calcium nodules was not described in any of the reports included in the present review, suggesting that this factor was either not evaluated or not considered. Also, a narrow aortic root with shallow sinuses of Valsalva leaving little room to accommodate the calcified native aortic leaflets after valve deployment might also be an important factor associated with coronary obstruction after TAVI. In this series, the mean aortic root diameter was approximately 28 mm, which was lower than the >30-mm diameter reported in previous studies evaluating aortic root geometry (33,35) (Fig. 2). However, most reports included in the present review evaluated the aortic root diameter by echocardiography, and it has been shown that echocardiography tends to underestimate aortic root diameters compared with multislice CT (34,44). Thus, we cannot draw firm conclusions about the role of aortic morphology, and in particular the degree of aortic root effacement, in relation to this complication.

Analysis of the clinical characteristics of the patients who suffered coronary obstruction after TAVI revealed a mean age (82.5 ± 7 years) and risk profile (mean logistic European System for Cardiac Operative Risk Evaluation score: 25.1 ± 12) similar to those reported in most previous TAVI studies (Fig. 1). However, up to 83% of the patients suffering this complication were women, and this is a significantly higher rate in comparison with the approximately 50% prevalence of women in most TAVI studies (Fig. 1). Moreover, it has been shown that women have a smaller aortic root (45); this, together with lower coronary ostia height, might partially explain the increased incidence

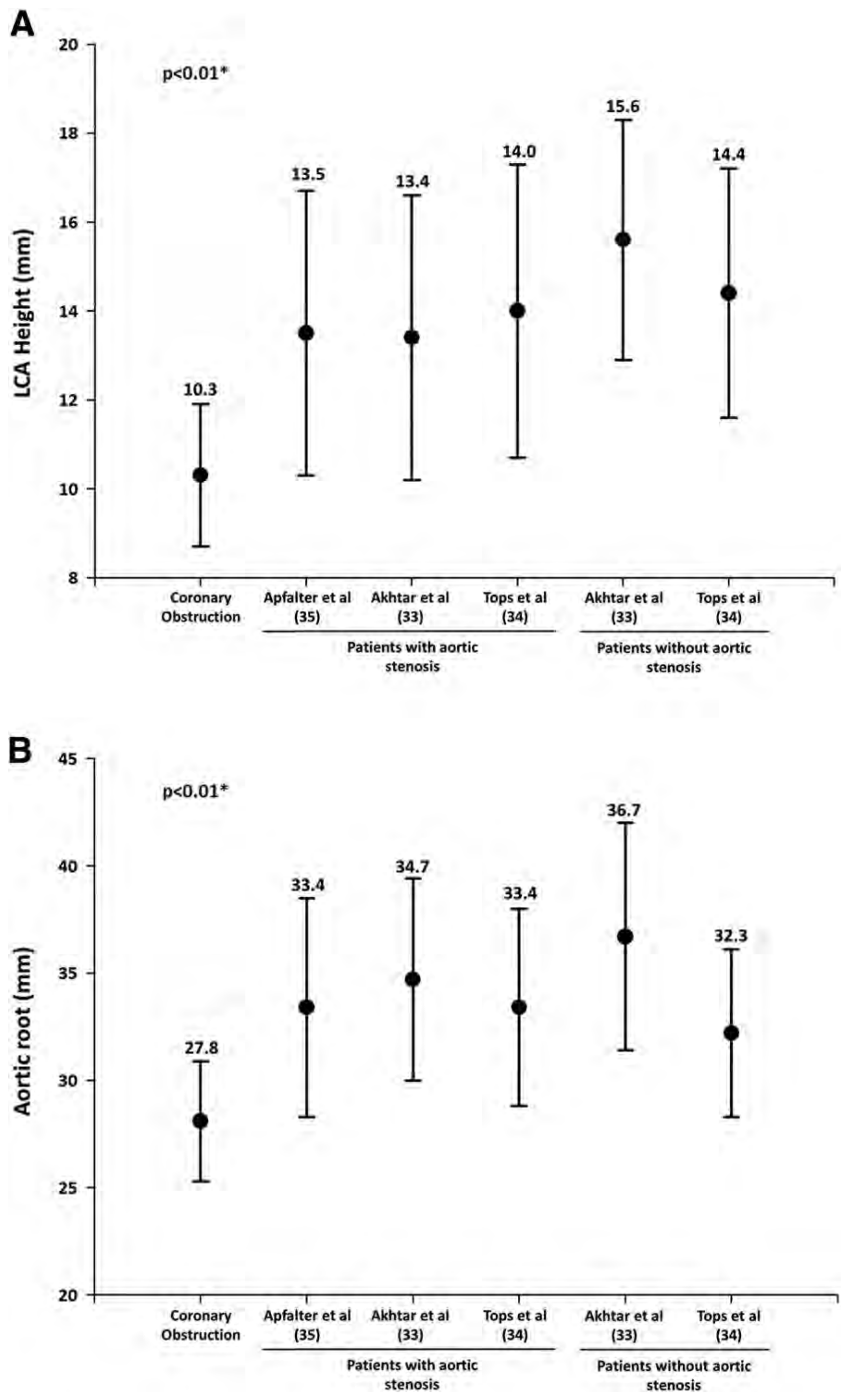

Figure 2. Computed Tomography Data

Mean values of the left coronary artery (LCA) height **(A)** and aortic root diameter **(B)** of patients with coronary obstruction after transcatheter aortic valve implantation compared with the values obtained from previous computed tomography studies, including patients with and without aortic stenosis (33–35). *Coronary obstruction versus other groups.

Table 3. Individual Data on Clinical Presentation and Management of Coronary Obstruction

		Clinical Presentation			Treatment						
Patient	Coronary Obstruction	Severe Hypotension	ST-Segment Changes	Ventricular Arrhythmias or CPR	PCI	CABG	Successful PCI	Stent Type	Need for Hemodynamic Support	Hospital Stay (days)	In-Hospital Death
1 (9)	Both	Yes	Yes	No	Yes	No	Yes	BMS	No	11	No
2 (10)	LCA	Yes	No	No	No	No	—	—	No	5	Yes
3 (11)	LCA	Yes	Yes	Yes	Yes	No	Yes	DES	No	5	No
4 (12)	LCA	Yes	Yes	Yes	Yes	No	Yes	BMS	Yes	13	No
5 (12)	RCA	Yes	Yes	No	Yes	Yes	No	—	Yes	12	No
6 (12)	RCA	Yes	Yes	Yes	Yes	No	Yes	—	No	14	No
7 (13)	LCA	Yes	Yes	No	Yes	No	Yes	DES	No	4	No
8 (13)	LCA	Yes	No	Yes	Yes	No	No	BMS	Yes	0	Yes
9 (13)	LCA	Yes	No	Yes	Yes	No	Yes	BMS	No	5	No
10 (13)	LCA	Yes	Yes	No	Yes	No	Yes	BMS	No	4	No
11 (13)	LCA	No	No	No	Yes	No	Yes	—	No	3	No
12 (14)	LCA	Yes	No	No	Yes	No	Yes	BMS	No	—	No
13 (15)	LCA	Yes	No	Yes	Yes	No	Yes	BMS	Yes	5	No
14 (16)	LCA	Yes	No	Yes	Yes	No	Yes	BMS	No	5	No
15 (17)	RCA	Yes	Yes	No	Yes	No	Yes	BMS	No	4	No
16 (18)	LCA	Yes	Yes	No	Yes	No	Yes	DES	No	—	No
17 (19)	LCA	Yes	Yes	Yes	Yes	No	Yes	DES	Yes	8	No
18 (20)	LCA	Yes	Yes	No	Yes	No	Yes	BMS	No	5	No
19 (21)	LCA	Yes	No	Yes	Yes	No	Yes	BMS	No	—	No
20 (22)	LCA	Yes	No	Yes	Yes	No	Yes	DES	No	11	No
21 (23)	LCA	Yes	Yes	No	Yes	No	Yes	Both	No	—	No
22 (24)	LCA	No	Yes	No	Yes	No	Yes	BMS	No	—	No
23 (25)	LCA	No	No	No	Yes	No	Yes	BMS	No	—	No
24 (26)	LCA	Yes	No	Yes	Yes	No	Yes	DES	Yes	—	No

BMS = bare-metal stent; CABG coronary artery bypass graft; CPR = cardiopulmonary resuscitation; DES = drug-eluting stent; LCA = left coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

of this complication among women. Also, the rate of prior CABG (4.2%) was much lower than in prior TAVI studies, confirming the "protective effect" of CABG against symptomatic coronary ostia obstruction.

With regard to procedural characteristics, most reported patients who suffered coronary obstruction after TAVI had received a balloon-expandable Edwards valve. Data from previous TAVI registries also showed a slightly higher rate of coronary obstruction after balloon-expandable (>0.4%) versus self-expandable (<0.2%) valve implantation (Table 5) (2–4,6–8). Although the frame characteristics of the transcatheter valves (straight stainless steel or cobalt chromium vs. nitinol) and the mechanisms for valve implantation (balloon-expandable vs. self-expandable) might partially explain these differences, the criteria with regard to minimal sinus of Valsalva diameter and coronary ostia height requirements differ between the 2 transcatheter valves (SAPIEN and CoreValve; Medtronic, Minneapolis, Minnesota), and this might also explain the higher rate of coronary obstruction observed with the Edwards valve system. Whereas no specific formal recommendation for sinus of Valsalva width and coronary ostia height is provided for the implantation of the Edwards valve, a recommendation of a sinus of Valsalva width ≥27 mm (for the 26-mm CoreValve) or ≥28 mm (for the 29-mm CoreValve) mm and a coronary height ≥14 mm is provided by the manufacturer for the implantation of the CoreValve system. These specific recommendations, although probably not followed strictly by all CoreValve implanting centers, might have prevented a significant number of coronary obstructions with the CoreValve system.

Clinical presentation and management of coronary obstruction after TAVI. The vast majority of patients presented with persistent severe hypotension after valve implantation, and approximately 50% and 25% of them also had ST-segment changes (approximately one-half of them with ST-segment elevation) and procedural ventricular arrhythmias, respectively. This clinical presentation could be explained by the fact that approximately 90% of the patients had LCA involvement, thus resulting in significant left ventricular ischemia. Therefore, it is of major clinical importance in the presence of persistent severe hypotension after valve implantation, even in the absence of ECG changes, that prompt echocardiography be performed to look for new segmental

Table 4. Clinical Presentation and Management of Coronary Obstruction

Obstructed coronary artery	
Left main	20 (83.3%)
Right	3 (12.5%)
Both coronary arteries	1 (4.2%)
Clinical presentation	
Severe maintained hypotension	21 (87.5%)
ST-segment changes	13 (54.2%)
ST-segment elevation	6 (25.0%)
Ventricular arrhythmias	6 (25.0%)
Treatment	
PCI attempted	23 (95.8%)
Successful	21 (91.3%)
Stent successfully implanted	19 (82.6%)
Guide-wire protection only	1 (4.4%)
Catheter manipulation removed the calcium	1 (4.4%)
Unsuccessful	2 (8.7%)
Wire crossing failure	1 (4.4%)
Stent implanted but no flow	1 (4.4%)
Postmortem diagnosis	1 (4.4%)
Type of stent	
BMS only	13 (65.0%)
DES only	6 (30.0%)
Both	1 (5.0%)
Complications	
Need for cardiopulmonary resuscitation	9 (37.5%)
Need for hemodynamic support	6 (25.0%)
Compression requiring 2nd stent	3 (13.4%)
Conversion to open heart surgery	2 (8.3%)
Restenosis	1 (4.2%)
In-hospital death	2 (8.3%)
Hospital stay length, days	7 ± 4

N = 24.
PCI = percutaneous coronary intervention.

abnormalities and/or coronary angiography to look for coronary obstruction. Interestingly, both in normal postmortem hearts and in a recent study examining the aortic root with multislice CT, the distance from the LCA ostium to the basal attachment point of the aortic valve leaflet was lower as compared with the right coronary ostium, which might explain why coronary obstruction after TAVI is more frequent on the left side (34,43).

The present study showed that PCI was the preferred strategy for the treatment of coronary obstruction after TAVI. It is noteworthy that PCI was feasible and associated with a 91.3% success rate. Bare-metal stents were used more frequently than drug-eluting stents, and there were no cases of stent thrombosis or need for repeat revascularization during the hospital stay. However, 3 patients (13%) needed a second stent due to significant compression of the first implanted stent unresponsive to balloon post-dilation. Hence, one might argue for the use of stents with higher radial force and routinely perform high-pressure post-dilation with a noncompliant balloon. The reasons for these findings are not yet understood; nonetheless, the struts from the valve frame and most likely external compression from the calcific native valve cusp might play an important role (24,25). Importantly, up to 25% and 8% of the patients required either mechanical hemodynamic support (cardiopulmonary bypass, intra-aortic balloon, tandem heart support) or conversion to open heart surgery, respectively, highlighting the importance of performing these procedures in highly experienced centers with cardiac surgery facilities.

Study limitations. The present study has the limitations inherent to a systematic review that collects only the information described in the publications. Therefore, there might be relevant information omitted in the publications that could shed some more light on this complication. Indeed, imaging data (especially on CT) was not available in all reported cases, and this prevented an appropriate evaluation of the characteristics of the patient determining a higher risk for the occurrence of this complication. In addition, all the papers found in the published data were either case reports or very small series, precluding comparison with the entire TAVI population at risk. Additionally, the reported patients might have tended to pursue a better outcome than those who were not published ("selection bias").

Conclusions

Coronary obstruction remains a rare but potentially life-threatening complication of TAVI. Baseline characteristics from reported cases suggest that this complication occurs more frequently in women with no prior CABG and in patients receiving a balloon-expandable valve. Future studies will have to confirm these data and elucidate whether the potential lower rate of coronary obstruction observed after self-expandable valve implantation is due to a transcatheter valve class effect or to differences between valve types with regard to pre-specified recommendations on coronary ostia height and aortic root dimensions. Also, although the 10-mm "safety cut-off" for coronary ostia height might help to prevent coronary obstruction during TAVI, approximately one-half of the patients who had this complication exhibited a coronary ostia height >10 mm, suggesting both that a higher "safety cut-off" might be required and that factors other than coronary height (dimensions of sinuses of Valsalva and/or severe valve calcification) might probably play an important role in the occurrence of this complication. The results of this study also suggest that the occurrence of persistent severe hypotension, irrespective of the presence or absence of ST-segment changes, immediately after valve implantation requires ruling out this complication. Importantly, PCI was a feasible and effective treatment in most cases, although the rates of additional hemodynamic support, conversion to open heart surgery, or stent compres-

Table 5. Data on Coronary Obstruction From Large TAVI Registries and the PARTNER Trial

Study	n	Valve/Approach	TF	TA	All Procedures	Cases SAPIEN	Cases CoreValve
ADVANCE (3)	996	CoreValve	0.1%	—	0.1%	—	1
Canadian (4)	345	Cribier-Edwards, SAPIEN, SAPIEN XT/49% TF, 51% TA	0.6%	1.1%	0.9%	3	—
FRANCE (2)	244	SAPIEN or CoreValve/66% TF, TS 5%, 29% TA	SAPIEN (2.1%) CoreValve (1.5%)	0%	1.2%	2	1
German (8)	670	SAPIEN or CoreValve/96% TF, 4% TA	—	—	0.1%	—	—
SOURCE (6)	1,038	SAPIEN/45% TF, 55% TA	0.7%	0.5%	0.6%	6	—
PARTNER (5)	348	SAPIEN/70.1% TF, 29.9% TA	0%	0%	0%	—	—
Source XT (7)	2,600	SAPIEN XT/63% TF, 34% TA	0.3%	0.3%	0.3%	8	—
Pooled studies			13/3,726 (0.35%)	8/1,833 (0.44%)	22/6,241 (0.35%)	19	2
SAPIEN					19/4,497 (0.42%)		
CoreValve					2/1,074 (0.19%)		

ADVANCE = Medtronic CoreValve study; FRANCE = FRench Aortic National CoreValve and Edwards registry; PARTNER = Placement of Aortic Transcatheter Valve trial; SOURCE = SAPIEN aortic bioprosthesis European outcome registry; TAVI = transcatheter aortic valve implantation; other abbreviations as in Table 1.

sion requiring the implantation of a second stent remained important. Future prospective studies, including consecutive series of TAVI patients with this complication, are needed to further evaluate the predictive factors and the most appropriate clinical management of this important complication of TAVI.

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Key Words: aortic stenosis ■ coronary obstruction ■ coronary occlusion ■ coronary stenosis ■ transcatheter aortic valve replacement ■ transcatheter heart valve.

APPENDIX E

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ORIGINAL INVESTIGATION

Transfemorally or Transapically Deployed Sapien Edwards Bioprosthesis Is Always Deformed

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Objective: *To study the impact of femoral compared to apical access on the Sapien-Edwards (SE) prosthesis deployment and geometry in patients treated with transcatheter aortic valve implantation (TAVI) for aortic stenosis.*
Background: *SE prosthesis deformation exists after its deployment through transfemoral (TF-TAVI) approach. However, no study comparing the deformation between TF-TAVI and transapical (TA-TAVI) approaches has yet been published.*
Methods: *Forty consecutive patients received TAVI with the SE prosthesis (TF-TAVI n = 25; TA-TAVI n = 15). A fluoroscopic analysis of the prosthesis was then performed. The stent frame geometry was assessed during deployment in the profile view, and after implantation in the profile and frontal views.*
Results: *Expansion kinetics revealed a triphasic stent deployment with both approaches; the aortic extremity being the first to open. After implantation, on the profile view, the stent shape was never rectangular (therefore never cylindrical) in both groups. It had a biconic shape in most of the patients (76% vs. 93.3% for TF-TAVI and TA-TAVI patients, respectively, P = 0.224) with a wider aortic extremity relative to the ventricular one. The frontal view analysis showed that circular deployment of the stent was never achieved. A greater leaflet to stent mismatch was noted in TA-TAVI patients, however, the difference was not statistically significant (12% vs. 33.3%, P = 0.126).*
Conclusion: *Fluoroscopically assessed, the geometry of SE prosthesis was never cylindrical after deployment, whatever the access for implantation was. Longitudinal deformation was greater after TF-TAVI whereas leaflet to stent mismatch tended to be more pronounced after TA-TAVI.* (J Interven Cardiol 2011;**:1–9)

Introduction

Elderly patients with severe degenerative aortic stenosis (AS), multiple comorbidities, and high-operative risk remain a challenge to surgical aortic valve replacement (AVR). These patients, who represent almost a third of patients with severe valvular lesions, are left to their natural history of AS that carries a significant rate of death.[1] In 2002, percutaneous implantation of a valved stent as treatment for severe AS was accomplished for the first time in humans.[2] Thereafter, transcatheter aortic valve implantation (TAVI) gained much interest and became a possible interventional treatment modality for inoperable patients or those refused to surgery. Yet, this remains a dynamic field of research and development prone to advances in prosthesis characteristics, delivery systems, and interventional technique of implantation. Two devices are under clinical investigation for TAVI. The Sapien-Edwards (SE) prosthesis (Edwards Lifesciences Inc., Irvine, CA, USA), which consists of three bovine pericardial leaflets mounted within a tubular, slotted, stainless steel, balloon-expandable stent, and the CoreValve Revalving System (CRS, Medtronic, Luxembourg, Luxembourg, UK), a self-expandable nitinol valve.

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The SE prosthesis is available in 23 and 26 mm sizes, delivered through 22F and 24F introducer sheaths, respectively, for the transfemoral (TF-TAVI) approach, and a 26F introducer sheath for the transapical (TA-TAVI) approach. In a previous human study, we showed that stent deformation occurs frequently after deployment in patients with severe AS.[3] This deformation of the stent is transmitted to valve leaflets leading to valve distortion. The latter may shorten the long-term durability of the valve mainly by increasing the amount of stress on some parts of the leaflets.[4] This finding has also been demonstrated to be true for the SE prosthesis after its implantation. In fact, based on a fluoroscopic morphologic analysis of the SE stent shape after TAVI through retrograde approach,[5] we found that stent deformation was always present, leading to a leaflet to stent mismatch in at least 17.5% of cases. Whether this deformation exists when the SE prosthesis is deployed through the TA-TAVI approach remains unknown. We sought in the current trial to study the kinetics of deployment of the SE valved stent, to study its final shape after implantation, and to draw a comparison between TF-TAVI and TA-TAVI approaches on these factors in 40 patients treated with TAVI using the same fluoroscopic morphologic parameters.

Methods

Patients. The population studied consisted of 40 consecutive patients with severe AS for whom surgical AVR was declined because of high operative risk. The patients underwent, between February 2008 and June 2009, a TAVI of the SE prosthesis. The retrograde TF-TAVI approach was used in 25 patients and the TA-TAVI approach in 15 patients. We analyzed retrospectively data regarding patients' characteristics, implantation procedure, deployment, and postdeployment measurements. The study was approved by the local institutional review board and all patients gave their written informed consent.

Procedure. The implantation technique of the SE prosthesis has been described previously.[6,7] The Retroflex 1 delivery system was used for the implantation of the valve in all patients (this delivery system is no longer in use and was replaced by the Retroflex 3 and thereafter the Novaflex system for deployment of the Sapien-XT prosthesis). The deployment of the valve was recorded in the long-axis view and digitized at a frequency of 30 frames/s. At the end of each procedure, 2 fluoroscopic views of the implanted valve were obtained, the *profile* (long-axis) view and the *frontal* (short-axis) view (Fig. 1).

Measurements. On the *profile* view, we measured (1) the diameter of the stent at the ventricular end (proximal diameter, P), (2) the diameter at the aortic end (distal diameter, D), and (3) the minimal or intermediate diameter (M) which is the smallest diameter located between both extremities of the stent. This diameter was identified by locating the most inner point on the external rim of stent left and right borders (Figs. 1A and C).[5] On the *frontal* view, points for measurements were placed at the external border of the stent projection. We identified at first the "commissural bands," i.e., the three points of the stent frame to which the leaflets are attached at their commissural level. The three "commissural bands" were easily identifiable on fluoroscopic views (Figs. 1B and D). Their projection described a triangle (Fig. 1). This triangle, in the "ideal'' case, must be an equilateral one. The length (L) of each side of the triangle was measured. A height from the middle of each side of the triangle was then drawn. The intersection of this segment with the most external rim of the stent was identified too. The length of this height (H) was measured for each side. The ratio L/2H was calculated. In case of circular stent deployment, this ratio is independent of the stent diameter and should be equal to tg $(\pi/3) \approx 1.73$. In opposition to this, alteration in the L/2H ratio would suggest a noncircular deployment of the stent— the higher the ratio, the lower the stent expansion relatively to the intercommissural distance. The longest side of the triangle was identified as Lmax and the shortest one as Lmin. The highest L/2H ratio is referred to as L/2Hmax and the lowest one as L/2Hmin.Values were reported as relative differences between the maximal and minimal dimension within the same stent and are therefore expressed as percentages, because of variations due to valve size, fluoroscopic magnification, and patient positioning or anatomy. Circular stent shape was defined as a stent having all three L/2H ratios within 10% of the theoretical value, i.e., 1.73 ± 0.17. Leaflet to stent mismatch was considered to be present if the relative difference between the longest and the shortest side (Lmax – Lmin/Lmin) within a same triangle exceeded 10%.[5] Results were compared between the TF-TAVI and TA-TAVI groups.

Kinetics of Deployment. The kinetics of deployment was studied in 33 patients. The Ps and Ds

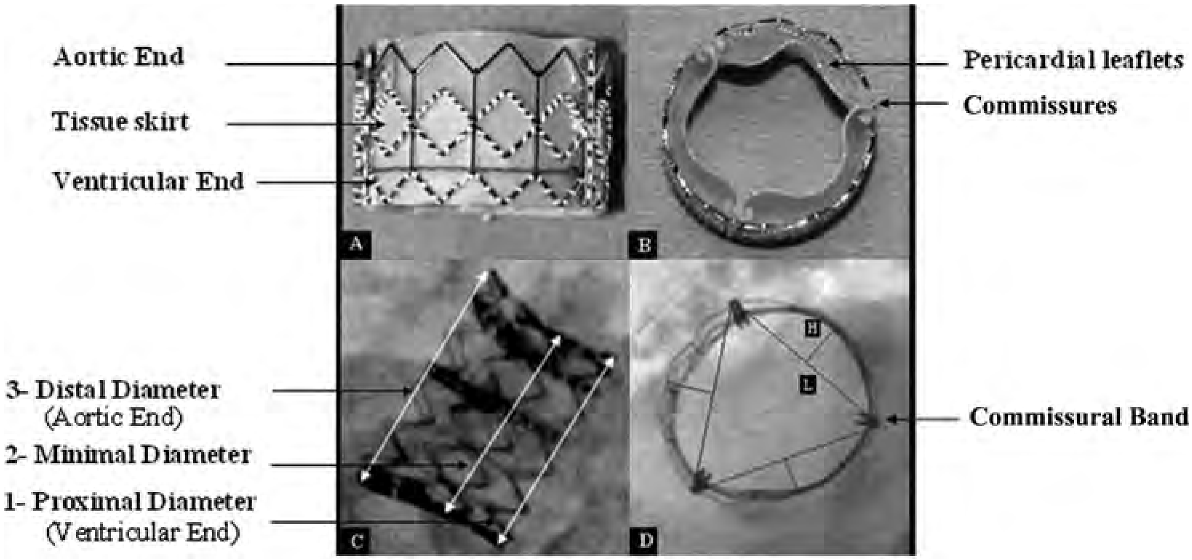

Figure 1. Sapien-Edwards prosthesis structure and fluoroscopic appearance after implantation. On the *profile* view (A, C) three diameters were measured. On the *frontal* view (B, D), the L/2H ratio was calculated. L/2H ≈ 1.73 in a perfectly deployed stent with a circular rim.

were measured sequentially every 0.23 seconds during balloon inflation. The expansion of both aortic and ventricular extremities of the stent was then studied and expressed as D/P ratio.

Statistical Methods. Continuous variables were expressed as median (range) and categorical variables as percentages. We used Fisher's exact test to compare categorical variables and the Mann-Whitney U test to compare continuous variables. Statistical significance was defined as $P < 0.05$.

Results

Patients. TAVI was successfully attempted in 40 patients with symptomatic AS and high surgical risk, 25 patients through the TF-TAVI approach, and 15 patients through the TA-TAVI approach. Preoperative clinical characteristics of the patients recruited are shown in Table 1. Echocardiographic characteristics are shown in Table 2. Median age was of 81 years (range, 61–91) for the TF-TAVI population and 80 (range, 66–91) for the TA-TAVI population. Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 21.6% and 28.9% for TF-TAVI and TA-TAVI patients, respectively. There were no significant differences between both groups concerning clinical and echocardiographic characteristics unless for more peripheral artery disease in TA-TAVI patients, 12% versus 53.3% ($P = 0.009$) and a higher left ventricle end-diastolic diameter in the TF-TAVI group.

Procedure. The size of the implanted SE prostheses was 23 ($n = 16$ for TF-TAVI and $n = 8$ for TA-TAVI) or 26 ($n = 9$ for TF-TAVI and $n = 7$ for TA-TAVI). Characteristics of TAVI procedure and results of the study parameters are shown in Table 3.

Profile view analysis. In all 40 patients, the stent shape on the *profile* view was never strictly rectangular; thus, the SE prosthesis never had a cylindrical conformation after implantation. The aortic extremity was larger than the ventricular one in all TF-TAVI patients and in most TA-TAVI patients ($n = 11$, 73.3%). Moreover, the "longitudinal" deformation of the prosthesis was more pronounced in the TF-TAVI group, where the median difference between the D and P diameters was significantly higher than in TA-TAVI patients: 8.1% (range, 1.4–14.3%) versus 3.7% (range, –5.1% to 12.4%) for TF-TAVI and TA-TAVI groups, respectively ($P = 0.003$). This deformation was present with both 23- and 26-mm prosthesis sizes regardless of the access adopted (Table 4), but the distal extremity of the stent was the widest among patients who received the 23-mm prosthesis: (D–P)/P of 8.2% (–2.3 to 13.9) versus 4.2 (–5.1 to 14.3) in the 23- and 26-mm sizes groups, respectively.

Two types of stent shapes could be identified on the *profile* view, biconic and conic shapes. The biconic

Table 1. Clinical Characteristics of the Study Population

Baseline Characteristics	TF-TAVI n (%) or Median (range)	TA-TAVI n (%) or Median (range)	P Value
Age (years)	81 (61–91)	80 (66–91)	0.955
Gender, M/F	15 (60.0)/10 (40.0)	7 (46.7)/8 (53.3)	0.517
Height (cm)	165 (147–174)	165 (154–176)	0.372
Weight (kg)	67.5 (40–114)	63 (52–87)	0.510
NYHA functional class			
II	13 (52)	8 (53.3)	1.000
III–IV	12 (48)	7 (46.7)	1.000
Logistic EuroSCORE (%)	21.6 (4.1–56.1)	28.9 (9.2–90.4)	0.142
Diabetes	8 (32)	5 (33.3)	1.000
Hypertension	14 (56)	11 (73.3)	0.329
Chronic renal failure (Crcl < 50 mL/min)	10 (40)	4 (26.7)	0.502
COPD	2 (8)	2 (13.3)	0.622
Coronary artery disease	17 (68)	12 (80.0)	0.486
Cerebrovascular disease	9 (36)	6 (40)	1.000
Previous cardiac surgery	8 (32)	7 (46.7)	0.502
History of chest irradiation	2 (8)	0 (0)	0.519
Peripheral artery disease	3 (12)	8 (53.3)	0.009

Data are reported as n (%) or median (range). TF-TAVI = transfemoral transcatheter aortic valve implantation; TA-TAVI = transapical transcatheter aortic valve implantation; NYHA = New York Heart Association; Crcl = creatinine clearance; COPD = chronic obstructive pulmonary disease.

form of the stent, with an aortic and ventricular extremity larger than the middle part of the stent, was noted in most of the patients ($n = 33$, 82.5%; Fig. 2).

Frontal view analysis. On the *frontal* view, the rim of the projected image of the stent was never strictly linear along its entire course, delineating a noncylindrical shape of the stent. In fact, a more or less extended segment of the rim was linear (reflecting good alignment with X rays) whereas the remaining was crescent like (Fig. 3). This aspect was due to the stent eversion that mainly affected the aortic extremity of the stent, as shown by the *profile* analysis. The stent projection was usually grossly circular or elliptic. The three commissural bands' projection described an easily identifiable triangle. The median relative difference between the longest and the shortest side (or L value) within a same triangle was of 4% (range, 0.7–23.5%) in TF-TAVI group versus 6.3% (range, 1.3–18.3%) in TA-TAVI group ($P = 0.128$). Leaflet to stent mismatch, i.e., Lmax – Lmin/Lmin > 10%, was present in 12% (3 cases) and 33.3% (5 cases) of TF-TAVI and TA-TAVI patients, respectively ($P = 0.126$). Similar leaflet to stent mismatch was present in both 23- and 26-mm prostheses. Figure 4 depicts the cumulative distribution of the L/2H ratio. This ratio was significantly higher than the theoretical value (median: 2.09 [range, 1.67–2.72] for TF-TAVI and 2.06 [1.39–3.31] for TA-TAVI vs. 1.73; $P < 0.001$ in both cases). For a given stent, the relative difference between the highest and the smallest value (three "L/2H" ratios were calculated for each stent) was as high as 52.6% (median 17.6%; range, 1.5–52.6%) for the TF-TAVI and 124.6% (median, 28.3%; range,

Table 2. Echocardiographic Characteristics of the Study Population

	TF-TAVI n (%) or Median (range)	TA-TAVI n (%) or Median (range)	P Value
AVA (cm^2)	0.6 (0.24–1)	0.625 (0.31–1)	0.466
Mean aortic gradient (mmHg)	55 (24–110)	47 (16–84)	0.703
Aortic annulus diameter (mm)	21 (18–27)	21.5 (19–25)	0.867
LVEF (%)	53 (17–77)	60 (24–76)	0.081
LVEF ≤ 30%	4 (16)	2 (13.3)	1.000
LVEDD (mm)	55 (34–68)	52 (40–62)	0.045
ST (mm)	12 (10–20)	13 (10–15)	0.846

Data are reported as n (%) or median (range).
AVA = aortic valve area; LVEF = left ventricle ejection fraction; LVEDD = left ventricle end-diastolic diameter; ST = septal thickness.
Other abbreviations as in Table 1.

Table 3. Procedure Characteristics and Fluoroscopic Measurements Results

Characteristic	TF-TAVI n (%) or Median (range)	TA-TAVI n (%) or Median (range)	P Value
SE 23	16 (64)	8 (53.3)	0.527
SE 26	9 (36)	7 (46.7)	
Biconic shape	19 (76)	14 (93.3)	0.224
Duration of deployment (s)	3.27 (1.87–5.37)	3.85 (2.8–4.67)	0.031
(D-M)/M (%)	9.8 (1.4–18)	6.5 (5.0–15.8)	0.035
(P-M)/M (%)	1.1 (0–5.9)	2.8 (0–10.7)	0.078
(D-P)/P (%)	8.1 (1.4–14.3)	3.7 (-5.1–12.4)	0.003
L/2H	2.09 (1.67–2.72)	2.06 (1.39–3.31)	0.279
(L/2Hmax – L/2Hmin)/L/2Hmin (%)	17.6 (1.5–52.6)	28.3 (2.3–124.6)	0.128
L/2H >1.73 (%)	96	82.2	0.019
(Lmax – Lmin)/Lmin (%)	4 (0.7–23.5)	6.3 (1.3–18.3)	0.128
(Lmax – Lmin)/Lmin >10%	3 (12%)	5 (33.3%)	0.126

Data are reported as n (%) or median (range).
SE = Sapien-Edwards prosthesis; D = distal diameter on *profile* view (aortic end); M = minimal diameter on *profile* view; P = proximal diameter on *profile* view (at ventricular end); L = intercommissural distance on *frontal* view; L/2Hmax = highest L/2H ratio for a given stent; L/2Hmin = lowest L/2H ratio for a given stent. Lmax = longest intercommissural distance within a given stent; Lmin = shortest intercommissural distance within a given stent
Other abbreviations as in Table 1.

2.3–124.6%) for the TA-TAVI approach. However, this difference was similar between both groups. According to the predefined parameter for circular deployment, none of the patients had a circular stent shape after implantation. In fact, 60% (n = 15) of TF-TAVI patients and 47% (n = 7) of TA-TAVI patients had all three L/2H ratios outside the 1.73 ± 0.17 interval (P = 0.517).

Kinetics of stent deployment. The deployment of the stent during balloon inflation was studied in 33 patients (25 TF-TAVI and 8 TA-TAVI patients). Complete stent deployment until reaching its peak dimensions was achieved in less than 4 seconds in both groups (Fig. 5). However, the deployment was faster in TF-TAVI patients (median 3.27 seconds for TF-TAVI; median 3.85 seconds for TA-TAVI, P = 0.031). At baseline (just before balloon inflation), the P was larger than D. This was probably due to the presence of a tissue skirt only at the proximal part of the stent. During balloon inflation, the deployment of the stent was nonuniform along its height in both groups. However, the same pattern of deployment was observed in TF-TAVI and TA-TAVI patients, with identification of 3 distinct phases during expansion. Through the first phase of expansion, during early balloon inflation, the aortic extremity of the stent expanded first,

Table 4. Fluoroscopic Measurements Results According to Prosthesis Size

Characteristic	23 mm n = 24 n (%) or Median (range)	26 mm n = 16 n (%) or Median (range)	P Value
TF-TAVI	16 (66.7)	9 (56.3)	0.527
Prosthesis size/aortic annulus diameter	1.1 (1.05–1.28)	1.08 (0.96–1.18)	0.078
(D–M)/M (%)	10 (5–18)	6 (1.4–18)	0.007
(P–M)/M (%)	1.4 (0–9)	1.8 (0–17)	0.580
(D–P)/P (%)	8.2 (–2.3–13.9)	4.2 (–5.1–14.3)	0.037
L/2H	2.11 (1.47–3.31)	2.04 (1.39–2.64)	0.346
(L/2Hmax – L/2Hmin)/L/2Hmin (%)	17.3 (1.5–124.6)	23.5 (7–59.3)	0.348
L/2H >1.73 (%)	93.1	87.5	0.344
(Lmax – Lmin)/Lmin (%)	6 (1–15)	4 (1.3–24)	0.600
(Lmax – Lmin)/Lmin >10%	4 (16.7%)	4 (25%)	0.690

Data are reported as n (%) or median (range).
Abbreviations as in Tables 1 and 3.

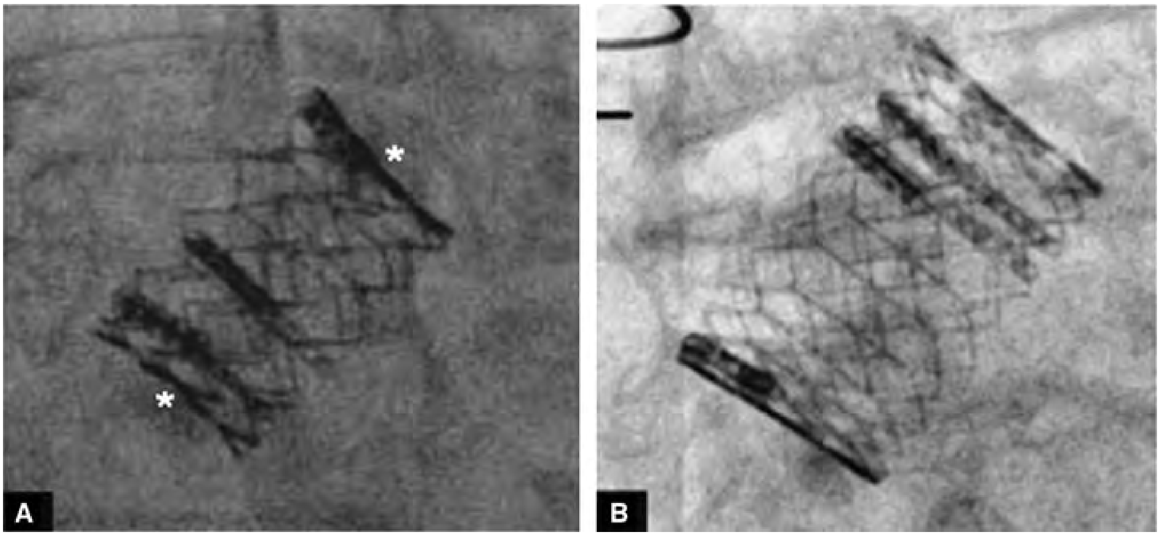

Figure 2. Sapien-Edwards stent shape after deployment. The biconic shape (panel 2A) is the most common shape of the Sapien-Edwards stent frame after implantation. In the conic form (panel 2B), the proximal extremity has the shortest diameter (* = waist zone).

so that the D/P ratio increased until reaching a peak value. TF-TAVI patients reached this peak earlier than TA-TAVI patients but the median difference was only of 0.23 seconds. The second phase was marked by a faster expansion of the ventricular extremity of the stent, thus the decrease in the D/P ratio. By the end of this phase, the ventricular and aortic extremities of the stent were equally distended in the TA-TAVI group with a D/P ratio equal to 1. During the third and last phase of expansion, the aortic and ventricular extremities of the stent expanded in a parallel fashion until reaching their peak values, thereby the D/P ratio remained stable. At the end of inflation, the D/P ratio of the TF-TAVI group remained higher than that of the TA-TAVI group, 1.07 versus 1.04, respectively ($P = 0.032$).

Discussion

Two main differences can be noted when comparing surgical AVR and TAVI procedures. During surgical AVR, the native calcified aortic valves are resected and the annulus is cleaned from its calcifications, preparing the environment for the prosthesis to be implanted, some thing that is not possible with TAVI procedures where valve calcifications are respected despite balloon aortic valvuloplasty before prosthesis implantation. The second difference resides in the implantation process. Surgically implanted bioprostheses are implanted in situ without previous preparation that could result in mechanical damage to leaflets. These 2 characteristics allow for a more physiological functioning of the bioprosthesis by keeping its circular ex vivo shape and by lowering the mechanical damage that could result from leaflet distortion. The latter may

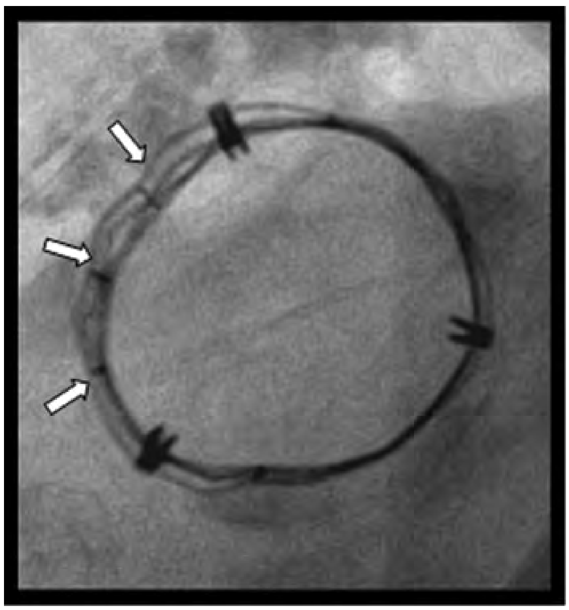

Figure 3. *Frontal* view projection of a deployed Sapien-Edwards (SE) prosthesis showing a crescent-like appearance (arrows) due to eversion of the distal (aortic) extremity of the stent.

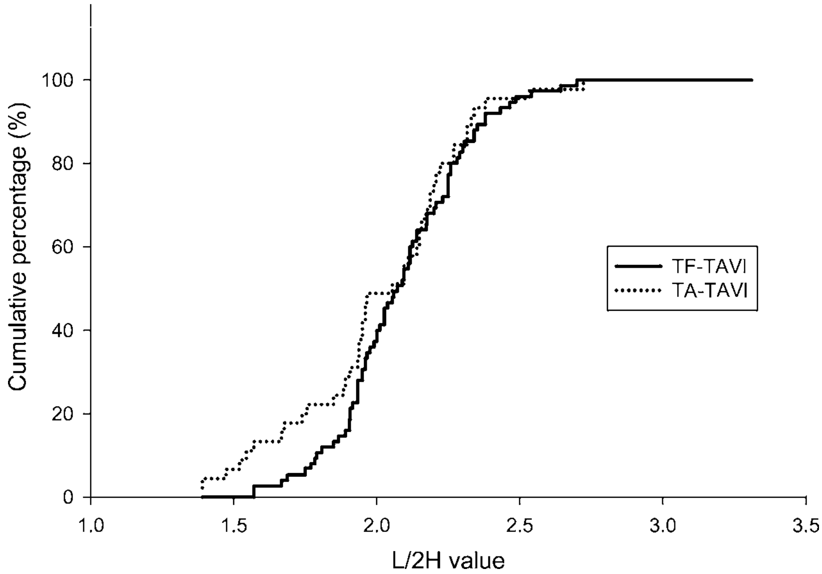

Figure 4. Cumulative distribution of L/2H ratio in the TF-TAVI and TA-TAVI groups. With both transfemoral and transapical approaches, the L/2H ratio was above the theoretical 1.73 value in most of the patients.

contribute to premature valve failure.[8] For optimal functioning, it is then mandatory that the percutaneously implanted valves reach their final ex vivo shape after implantation, i.e., an adequately sized cylindrical shape for the SE prosthesis. However, due to the aortic environment made of the heavily calcified native valves, valved stents are subject to considerable stress during their expansion that could lead to stent deformations, a noncircular stent shape after implantation and consequently in leaflets distortions as we have shown in our previous study.[3] Indeed, in a fluoroscopic analysis of SE prosthesis geometry after implantation, we have found that leaflet to stent mismatch as a result of stent deformation is not uncommon, where it occurred in at least 17.5% of patients who underwent TAVI with the SE prosthesis through a TF-TAVI retrograde approach.[5] To the best of our knowledge, this is the first study to compare the deployment and geometry of the SE prosthesis through TF-TAVI and TA-TAVI approaches. It is based on a fluoroscopic analysis of the prosthesis metal frame. Fluoroscopy is readily applicable immediately after valve implantation. It allows also a good visualization of the stent frame, a thing that is difficult to achieve with TTE or TEE due to reflections of the ultrasounds by the displaced calcified leaflets and the metallic stent frame. Furthermore, the

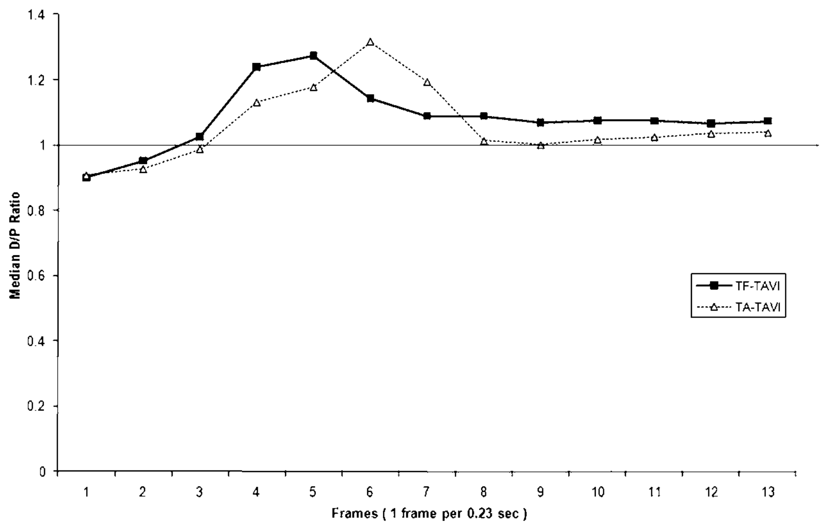

Figure 5. Kinetics of the Sapien-Edwards prosthesis expansion. Triphasic stent expansion pattern during balloon inflation with both transfemoral (TF-TAVI) and transapical approaches (TA-TAVI). D = distal diameter (aortic end); P = proximal diameter (ventricular end).

specific design of the SE prosthesis allows evaluation of commisures disposition owing to the visualization of the commissural "bands." There are anecdotal descriptions of multidetector row-computed tomography (MDCT) studies of deployed valved stent (VS).[6,7,9,10] A major potential advantage of this exam is the ability to analyze cross-sections performed at different levels of the valved stent. Another advantage of the computed tomography (CT) scan is to provide reliable measurements of the deployed valve. But still, methods used to evaluate the deployment of the stent depend on a visual assessment or vague criterion such as eccentricity indexes. An important finding of the present study was that circular deployment of the SE prosthesis was never observed, neither through TF-TAVI deployment nor through TA-TAVI one. In fact, most of the patients had all three L/2H ratios far from the theoretical value. This observation is discordant with the one described by Delgado et al.[10] where circular deployment of the SE prosthesis on MDCT analysis was found in 86% of all patients. We believe that eccentricity indexes based on measurements of two orthogonal diameters (short diameter/long diameter) are interesting to have a general idea about the stent shape but are not accurate enough to define circular deployment, because they are based on "fictive'' diameters and they may miss local stent deformations that exist (between "points" used to determine those diameters). It is then possible to have an eccentricity index equal to 1 and still a noncircular deployment. Another finding of the present study is that the leaflet to stent mismatch, as shown by a relative difference between the largest and smallest intercommissural distance within a same stent exceeding 10%, occurred more frequently with the TA-TAVI approach. However, the difference between both groups was not statistically significant (12% for TF-TAVI vs. 33.3% for TA-TAVI, $P = 0.126$). The L/2H ratio was higher than the theoretical value in both TF-TAVI and TA-TAVI patients. This implies that stent expansion was reduced compared to the intercommissural distance. If the movement of the free edge of the corresponding leaflet is not restricted (which is the case when the intercommissural distance is normal or even reduced), then this leaflet may hit the stent frame during each valve opening. This repeated contact of the leaflet with the stent frame during systolic valve opening has been observed on echocardiographic exams following valve implantation in some of our patients and might be responsible for a traumatic injury and more rapid deterioration of the leaflet in the long run. The kinetics study of the SE prosthesis expansion during balloon inflation revealed a nonuniform stent deployment. The triphasic pattern of expansion was found with both approaches, the expansion of the ventricular extremity of the stent being delayed relatively to the aortic one. The excessive "rigidity" of the proximal part of the prosthesis is probably due to the presence of a fabric skirt and of sutures between the skirt, the pericardial tissue, and the stent frame. Since valve expansion is driven by balloon inflation, any difference in rigidity between the proximal (stiffer) and the distal part of the prosthesis will tend to induce a relative overexpansion of the distal stent extremity. Although this hypothesis was consistent with our data (mean D greater than the proximal one in both groups), one cannot exclude a role for the design of the balloon in the pathogenesis of the final stent deformation. Better understanding of the respective role of the prosthesis and balloon design on the occurrence of stent deformation is required since poor stent deployment may have a negative impact on valve durability.

Conclusions

In summary, this fluoroscopic study of the SE prosthesis, one of the two currently available VS with the communauté européenne (CE)-mark approval for TAVI, revealed that this prosthesis did not have a cylindrical deployment, whether it is deployed through a TF-TAVI or a TA-TAVI approach. It also showed a more pronounced "longitudinal" deformation of the prosthesis in the TF-TAVI group and a tendency toward a higher leaflet to stent mismatch when the prosthesis was deployed through the TA-TAVI approach, where mismatch was seen in at least 33.3% of cases. The clinical impact of these new data will have to be determined.

Disclosure

None, except for Dr. Zegdi who is a stockowner of a company (named Cormove, Ivry le Temple, France) developing a new percutaneous valve.

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APPENDIX F

Edwards SAPIEN XT

• Transcatheter Heart Valve with the NovaFlex+ Transfemoral Kit
• Kateterinförd hjärtklaff med NovaFlex+ transfemoral-sats
• Transkateterhjerteklap (THV) med NovaFlex+ transfemoralsæt

DIRECTORY

English

Instructions For Use

Implantation of transcatheter heart valves shall be performed by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Product Name	23 mm System	26 mm System	29 mm System
	Model/REF		
NovaFlex+ Transfemoral Kit, comprised of the following:			
Edwards SAPIEN XT Transcatheter Heart Valve	9300TFX (23 mm)	9300TFX (26 mm)	9300TFX (29 mm)
NovaFlex+ Delivery System[1]	9355FS23	9355FS26	9355FS29
Edwards Expandable Introducer Sheath Set	916ES23	918ES26	920ES29
RetroFlex Dilator Kit	9100DKS		
Edwards Transfemoral Balloon Catheter	9350BC20	9350BC23	9350BC25
Crimper	9350CR		
Atrion QL2530 Inflation Device	96402		
Atrion QL38 Locking Syringe Device			96406
[1] Includes the Qualcrimp Crimping Accessory, 9300QC and 2-piece Crimp Stopper			

1.0 Device Description

- **Edwards SAPIEN XT Transcatheter Heart Valve (Figure 1)**

The Edwards SAPIEN XT transcatheter heart valve (THV or bioprosthesis) is comprised of a balloon-expandable, radiopaque, cobalt chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) fabric. It is treated according to the Edwards ThermaFix process, and is packaged and terminally sterilized in glutaraldehyde.

The THV is intended to be implanted in a native annulus size range comparable to the following transesophageal echocardiography (TEE) measurements:

Native Valve Annulus Size	Bioprosthesis Size
18–22 mm	23 mm
21–25 mm	26 mm
24–27 mm	29 mm

- **Qualcrimp Crimping Accessory (Figure 2)**

The Qualcrimp crimping accessory (packaged with the NovaFlex+ delivery system) is used during crimping of the THV.

- **NovaFlex+ Delivery System (Figures 3a, 3b, 3c)**

The NovaFlex+ delivery system includes a handle that provides a Flex Wheel for articulation of the Flex Catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, and a Balloon Catheter for deployment of the THV. The handle contains a Flex Indicator that shows whether or not the Flex Catheter is articulated, a Valve Alignment Wheel for fine adjustment of the THV during Valve Alignment, a Press/Release Button that enables movement between handle positions, and a flush port to flush the Flex Catheter. A stylet is included within the guidewire lumen of the delivery system. The Balloon Catheter has radiopaque Valve Alignment Markers defining the Valve Alignment Position and the working length of the balloon. A radiopaque Double Marker proximal to the balloon indicates the Flex Catheter position during deployment.

The inflation parameters for THV deployment are:

Model	Nominal Balloon Diameter	Nominal Inflation Volume	Rated Burst Pressure (RBP)
9355FS23	23 mm	17 ml	7 atm (709 kPa)
9355FS26	26 mm	22 ml	7 atm (709 kPa)
9355FS29	29 mm	33 ml	7 atm (709 kPa)

The following table identifies the access vessel diameters that should be used for delivery system access. Access vessels should be without severe obstructive calcification or severe tortuosity.

Ilio-Femoral Vessel Diameter	Delivery System
≥6.0 mm	23 mm
≥6.5 mm	26 mm
≥7.0 mm	29 mm

- **Edwards Expandable Introducer Sheath Set**

Refer to Edwards Expandable Introducer Sheath Set instructions for use.

- **RetroFlex Dilator Kit (Figure 4)**

The RetroFlex dilator kit contains a set of hydrophilically coated tapered dilators used for arterial dilatation.

- **Edwards Transfemoral Balloon Catheter**

Refer to Edwards Transfemoral Balloon Catheter instructions for use.

- **Crimper (Figure 5)**

The crimper reduces the diameter of the THV to mount it to the delivery system. The crimper is comprised of a compression mechanism that is closed with a handle located on the housing. The crimper includes a 2-piece Crimp Stopper (packaged with the delivery system) used to correctly crimp the THV.

- **Atrion QL2530 or QL38 Device**

The Atrion QL2530 or QL38 devices are used during native valve predilation and THV deployment.

2.0 Indications

The Edwards SAPIEN XT THV, NovaFlex+ delivery system and accessories are indicated for use in patients with symptomatic severe calcific aortic stenosis requiring aortic valve replacement (AVR), who have an estimated operative/procedural mortality risk ≥15% as assessed by a risk tool such as the Logistic EuroSCORE or STS-PROM.

3.0 Contraindications

Use of the Edwards SAPIEN XT THV with the NovaFlex+ delivery system and accessories is contraindicated in patients with:

- Congenital unicuspid or congenital bicuspid aortic valve;
- evidence of intracardiac mass, thrombus, vegetation, active infection or endocarditis;
- inability to tolerate anticoagulation/antiplatelet therapy.

4.0 Warnings

- The devices are designed, intended, and distributed for single use only. Do not resterilize or reuse the devices. There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.
- Incorrect sizing of the THV may lead to paravalvular leak, migration, and/or annular rupture.
- Accelerated deterioration of the THV may occur in patients with an altered calcium metabolism.
- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- The THV must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic saline solution. THV leaflets mishandled or damaged during any part of the procedure will require replacement of the THV.
- Patients with pre-existing mitral valve devices should be carefully assessed before implantation of the THV to ensure proper THV positioning and deployment.
- Patients presenting with combination AV low flow, low gradient should undergo additional evaluation to establish the degree of aortic stenosis.
- Caution should be exercised in implanting a THV in patients with clinically significant coronary artery disease.
- The safety of the THV implantation has not been established in patients who have:
    - o Pre-existing prosthetic heart valve in the aortic position
    - o Severe ventricular dysfunction with ejection fraction <20%
    - o Hypertrophic cardiomyopathy with or without obstruction
- Do not use the THV if the tamper evident seal is broken, the container is damaged, leaking, the glutaraldehyde storage solution does not completely cover the THV, the temperature indicator has been activated, the THV is damaged, or the expiration date has elapsed.
- Do not mishandle the delivery system and accessories or use them if the packing or any components are not sterile, have been opened or damaged (e.g. kinked or stretched), or the expiration date has elapsed.

5.0 Precautions

- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Material Safety Data Sheet available from Edwards Lifesciences.
- Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.
- THV recipients should be maintained on anticoagulant/antiplatelet therapy, as determined by their physician.
- Long-term durability has not been established for the THV. Regular medical follow-up is advised to evaluate valve performance.

6.0 Potential Adverse Events

Complications associated with standard cardiac catheterization, balloon valvuloplasty (BAV), and the use of anesthesia include but are not limited to:

- Abnormal lab values; allergic reaction to anesthesia or to contrast media; anemia including hemolytic anemia; angina; arrhythmia; heart murmur; bleeding; cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention; conduction system injury which may require a permanent pacemaker; death; embolization including air, calcific valve material or thrombus; exercise intolerance or weakness; femoral AV fistula or pseudoaneurysm; fever; heart failure; hematoma; hemorrhage requiring transfusion or intervention; hypertension/hypotension; infection including septicemia and endocarditis; inflammation; myocardial infarction; pain or changes at the access site; paralysis; pericardial effusion/cardiac tamponade; permanent disability; pleural effusion; pulmonary edema; renal failure; renal insufficiency; reoperation; restenosis; retroperitoneal bleed; stroke/transient ischemic attack/clusters/or neurological changes; syncope; systemic peripheral ischemia/nerve injury.

In addition to the risks listed above, additional potential risks specifically associated with aortic valve replacement and bioprosthetic heart valves include, but may not be limited to, the following:

- Cardiac failure/low cardiac output; cardiac arrest; cardiogenic shock; coronary flow obstruction/transvalvular flow disturbances; device degeneration; device explant; device embolization; device migration or malposition requiring intervention; device thrombosis requiring intervention; emergency cardiac surgery; hemolysis; hemorrhage; injury at site of venous or arterial access that may require repair; non-emergent reoperation; nonstructural dysfunction; paravalvular or transvalvular leak; potential coronary obstruction due to severe bulky calcification involving the left or right cusps of the aortic valve; structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent post, leaflet retraction, suture line disruption of components of a prosthetic valve, chordal rupture, thickening, stenosis, or other); valve regurgitation; valve stenosis; valvular thrombosis; valve implanted in unintended location.

7.0 Directions for Use

7.1 Required Equipment

- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.89 mm (0.035 inch) extra-stiff guidewire
- Pacemaker (PM) and pacing lead
- NovaFlex+ Transfemoral Kit
  - Edwards SAPIEN XT THV
  - NovaFlex+ Delivery System
  - Edwards Expandable Introducer Sheath Set
  - RetroFlex Dilator Kit
  - Edwards Transfemoral Balloon catheter or equivalent
  - Crimper
  - Atrion QL2530 or QL38 device (x2)
- Sterile rinsing containers; sterile physiological saline solution; sterile heparinized saline solution, and diluted radiopaque contrast medium (15:85 medium to saline dilution)
- Sterile table for THV and device preparation
- 20 ml syringe or larger
- 50 ml syringe or larger
- High-pressure 3-way stopcock (x2)

7.2 THV Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 THV Rinsing Procedure

The THV is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid, leakage, or broken or missing seals).

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 ml of sterile physiologic saline to thoroughly rinse the glutaraldehyde sterilant from the THV.
2	The THV is contained in the jar within a holder. Carefully remove the THV/holder assembly from the jar without touching the tissue. The holder is tagged with the THV serial identification number, which must be verified with the number on the jar lid and recorded in the patient information documents. Inspect the THV for any signs of damage to the frame or tissue.
3	Rinse the THV as follows: Place the THV/holder assembly in the first bowl, ensuring the saline solution completely covers the THV and holder. With the THV and holder submerged, **gently** swirl the THV and holder back and forth for a minimum of 1 minute. Repeat this process in the second bowl for a minimum of 1 minute. The THV should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: Do not allow the THV to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the THV. Care must be taken to ensure that the identification tag does not come in contact with and damage the tissue. No other objects should be placed in the rinse bowls.**

7.2.2 Prepare the System

Step	Procedure
1	Visually inspect all the components for damage. Ensure the NovaFlex+ delivery system is fully unflexed and the Valve Alignment Wheel is flush to the handle.
2	Prime and flush the guidewire lumen of the introducer and dilators with heparinized saline. Flush through the flush port of the introducer sheath and delivery system. Hydrate the length of the dilators and introducer.
3	Carefully remove the distal balloon cover from the delivery system. Place the delivery system into the Default Position and make sure that the flex catheter tip is covered by the proximal balloon cover.
4	Unscrew the loader cap from the loader and flush the loader cap with heparinized saline.
5	Place the loader cap onto the delivery system with the inside of the cap oriented towards the distal tip. Bring the delivery system out of Default Position and back into the packaged position with the device handle adjacent to the Y-connector. Carefully peel off the proximal balloon cover over the blue section of the balloon shaft.
6	Attach a 3-way stopcock to the balloon inflation port. Fill a 50 ml or larger syringe with 10–20 ml of diluted contrast medium and attach to the 3-way stopcock.

Step	Procedure
7	Fill the appropriate Atrion device with excess volume relative to the indicated inflation volume. Lock and attach to the 3-way stopcock.
8	Pull vacuum with the 50 ml or larger syringe to remove air. Repeat until all air bubbles are removed from the system. Slowly release the plunger to ensure that the contrast medium enters the lumen of the delivery system. Leave zero-pressure in the system.
9	With the knob of the Atrion device, remove the contrast medium into the syringe to achieve the appropriate volume required to deploy the THV, per the following:
10	After opening the stopcock, verify that the inflation volume is correct. **CAUTION: Maintain the Atrion device in the locked position until THV deployment.**

Delivery System	THV	Inflation Volume
Model 9355FS23	23 mm	17 ml
Model 9355FS26	26 mm	22 ml
Model 9355FS29	29 mm	33 ml

7.2.3 Mount and Crimp the THV on the Delivery System

Step	Procedure
1	Set up two (2) sterile bowls with at least 100 ml of sterile physiological saline to thoroughly rinse the Qualcrimp crimping accessory.
2	Completely submerge the Qualcrimp crimping accessory in the first bowl and gently compress it to ensure complete saline absorption. Slowly swirl the Qualcrimp crimping accessory for a minimum of 1 minute. Repeat this process in the second bowl.
3	Remove the THV from the holder and remove the ID tag.
4	Attach the 2-piece Crimp Stopper to the base of the crimper and click into place.
5	Starting with the crimper in the open position, gradually crimp the THV to a diameter of approximately 21 mm until it fits inside the Qualcrimp crimping accessory.
6	Place the Qualcrimp crimping accessory over the THV orienting the skirt of the Qualcrimp crimping accessory towards the inflow (cloth covered end) of the THV.
7	Place the THV and Qualcrimp in crimper aperture. Insert the delivery system coaxially within the THV in the Valve Crimp Section of the delivery system (Figure 3a – 2–3 mm distal to the blue balloon shaft) with the inflow of the THV towards the distal end of the delivery system.
8	Center the balloon shaft coaxially within the valve. Crimp the THV until it reaches the Qualcrimp Stop.
9	Gently remove the Qualcrimp crimping accessory from the THV and Qualcrimp Stop from the 2-piece Crimp Stopper, leaving the Final Stop in place.
10	Fully crimp the THV until it reaches the Final Stop. **NOTE: Ensure that the Valve Crimp Section (Figure 3a) is coaxial within the THV.**
11	Repeat the full crimp of the THV.
12	Pull the balloon shaft until it is locked in the Default Position.
13	Flush the loader with heparinized saline. Immediately advance the THV into the loader until the tapered tip of the delivery system is exposed. **CAUTION: To prevent possible leaflet damage, the THV should not remain fully crimped and/or in the loader for over 15 minutes.**
14	Attach the loader cap to the loader and re-flush the Flex Catheter. Remove the stylet and flush the guidewire lumen of the delivery system. **CAUTION: The physician must verify correct orientation of the THV prior to its implantation; the inflow (cloth covered end) of the THV should be oriented distally towards the tapered tip.**

7.3 Native Valve Predilation and THV Delivery

Native valve predilation and prosthetic valve delivery should be performed under local and/or general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

Administer heparin to maintain the ACT at ≥250 sec.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the view.
2	Evaluate the distance of the left and right coronary ostia from the aortic annulus in relation to the THV frame height.
3	Introduce a pacemaker (PM) lead until its distal end is positioned in the right ventricle.
4	Set the stimulation parameters, and test pacing.

7.3.2 Native Valve Predilation

Refer to Edwards Transfemoral Balloon Catheter instructions for use.

CAUTION: Prosthetic valve implantation should not be carried out if the balloon cannot be fully inflated during predilation.

7.3.3 THV Delivery

Step	Procedure
1	Predilate the femoro-iliac vessel using the RetroFlex dilator kit by advancing increasing sized dilators over the guidewire until the appropriate diameter is reached. Advance the maximum possible length of the dilator over the guidewire while following its progression on fluoroscopy.

Step	Procedure
2	Prepare and introduce the introducer sheath per its instructions for use.
3	Insert the loader assembly into the introducer sheath until the loader stops.
4	Advance the NovaFlex+ delivery system with the Edwards logo facing up through the introducer sheath until the THV exits the sheath. **NOTE: Maintain the proper orientation of the flex catheter (with the Edwards logo facing up) throughout the procedure.** **CAUTION: The THV should not be advanced through the introducer sheath if the sheath tip is not past the aortic bifurcation.** **CAUTION: To prevent possible leaflet damage, the THV should not remain in the introducer sheath for over 2 minutes.**
5	In a straight section of the descending aorta, initiate valve alignment by pressing the Press/Release button, pulling back the balloon catheter, and releasing the button. Continue pulling back the balloon catheter until the delivery system locks into the Valve Alignment Position (Refer to **Figure 3c**). Utilize the Valve Alignment Wheel to center the THV between the Valve Alignment Markers. **NOTE: Do not turn the Valve Alignment Wheel if the delivery system is not locked in the Valve Alignment Position.** **WARNING: Do not position the THV past the distal Valve Alignment marker. This will prevent proper valve deployment.** **CAUTION: Maintain guidewire position in the left ventricle during valve alignment.**
6	Utilize the Flex Wheel to traverse the aortic arch and cross the native valve. **NOTE: Verify the Edwards logo is facing up. The delivery system articulates in a direction opposite from the flush port.**
7	If additional working length is needed, remove the loader by unscrewing the loader cap and peeling the loader tubing from the delivery system.
8	Retract the Flex Catheter to the Double Marker and position the THV.
9	Verify the correct position of the THV with respect to the native valve.
10	Ensure the valve is correctly aligned between the markers.
11	Begin THV deployment: • Unlock the Atrion device. • Ensure hemodynamic stability is established and begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the THV by inflating the balloon with the entire volume in the Atrion device, hold for 3 seconds and confirm that the barrel of the Atrion device is empty to ensure complete inflation of the balloon. • Deflate the balloon. When the balloon catheter has been completely deflated turn off the pacemaker.

7.3.4 System Removal

Step	Procedure
1	Unflex the delivery system while traversing the aortic arch. Retract the Flex Catheter until it locks in the Default Position and remove it from the sheath. **CAUTION: Patient injury could occur if the delivery system is not de-articulated prior to removal.**

7.4 Verification of Prosthetic Valve Position and Measurements

Measure and record hemodynamic parameters.

Step	Procedure
1	Perform a supra aortic angiogram to evaluate device performance and coronary patency.
2	Measure and record the transvalvular pressure gradients.
3	Remove all devices when the ACT level is appropriate (e.g., reaches <150 sec). Refer to the introducer sheath instructions for use for device removal.
4	Close the access site.

8.0 How Supplied

The THV is supplied sterile and nonpyrogenic packaged in buffered glutaraldehyde, in a plastic jar to which a tamper evident seal has been applied. Each jar is shipped in a shelf box containing a temperature indicator to detect exposure of the THV to extreme temperature. The shelf box is enclosed in Styrofoam prior to shipping.

The delivery system and accessories are supplied pouched and sterilized by ethylene oxide. The Atrion QL2530 and QL38 devices are supplied in a thermoformed peel tray and sterilized by ethylene oxide.

8.1 Storage

The THV must be stored at 10°C–25°C (50°F–77°F). The delivery system and accessories should be stored in a cool, dry place.

9.0 MR Safety

MR Conditional

Non-clinical testing has demonstrated that the THV (implant) is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3.0 Tesla (T).
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole body averaged specific absorption rate (WB-SAR) of 2.0 W/kg for 15 minutes of scanning.
- Normal mode of operation, as defined in IEC 60601-2-33 Ed.2.0, of the MR system.

In non-clinical testing and analysis, the implant was determined to produce an *in vivo* temperature rise of less than 1.3°C above background for a WB-SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5 T whole body coil from a GE Signa MR system. The projected *in vivo* rise above background was 1.5°C for a WB-SAR of 2.0 W/kg in a 3.0 T GE Signa HDxt 3T MR system. These calculations overestimate the true *in vivo* rise, since the cooling effects of blood are not considered.

The image artifact extends as far as 10 mm from the implant for spin echo images and 30 mm for gradient echo images when scanned in non-clinical testing using a 3.0 T GE Signa HDx MR system.

The implant has not been evaluated in MR systems other than 1.5 T or 3.0 T.

10.0 Patient Information

A patient registration form is provided with each THV. After implantation, please complete all requested information. The serial number may be found on the package and on the identification tag attached to the THV. Return the original form to the Edwards Lifesciences address indicated on the form and provide the temporary identification card to the patient prior to discharge.

11.0 Recovered THV and Device Disposal

The explanted THV should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Used devices may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 5,411,552; 5,931,969; 6,210,957; 6,214,054; 6,547,827; 6,561,970; 6,893,460; 6,908,481; 7,214,344; 7,510,575; 7,530,253; 7,585,321; 7,780,723; and RE40570 and corresponding foreign patents. Additional patents are pending.

Svenska

Bruksanvisning

Implantation av kateterinförda hjärtklaffar får endast utföras av läkare som genomgått Edwards Lifesciences utbildning. Den implanterande läkaren ska ha erfarenhet av ballongvalvuloplastik på aorta.

Produktnamn	23 mm system	26 mm system	29 mm system
	Modell/Ref		
NovaFlex+ transfemoral-sats, bestående av följande:			
Edwards SAPIEN XT kateterinförd hjärtklaff	9300TFX (23 mm)	9300TFX (26 mm)	9300TFX (29 mm)
NovaFlex+ införingssystem[1]	9355FS23	9355FS26	9355FS29
Edwards sats med expanderbar införarhylsa	916ES23	918ES26	920ES29
RetroFlex dilatatorsats	9100DKS		
Edwards transfemoral ballongkateter	9350BC20	9350BC23	9350BC25
Krimpverktyg	9350CR		
Atrion QL2530 uppblåsningsanordning	96402		
Atrion QL38-låsspruteanordning			96406
[1] Inkluderar Qualcrimp krimptillbehör 9300QC och 2-delat krimpstopp			

1.0 Beskrivning av enheten

- **Edwards SAPIEN XT kateterinförd hjärtklaff (Figur 1)**

Edwards SAPIEN XT kateterinförd hjärtklaff (THV eller bioprotes) består av en ballong-expanderbar, röntgentät klaff av trebladig bovin perikardiell vävnad med koboltkromram och polyetylentereftalatväv (PET). Den är behandlad enligt Edwards ThermaFix-processen, förpackad, och slutligen steriliserad i glutaraldehyd.

THV är avsedd att implanteras i ett storleksintervall på nativ annulus, jämförbart med följande transesofageala ekokardiografi- (TEE) mätningar:

Storlek på den nativa klaffens annulus	Bioprotesstorlek
18–22 mm	23 mm
21–25 mm	26 mm
24–27 mm	29 mm

- **Qualcrimp krimptillbehör (Figur 2)**

Qualcrimp krimptillbehör (förpackade med NovaFlex+ införingssystem) används under krimpning av THV.

- **NovaFlex+ införingssystem (Figurer 3a, 3b, 3c)**

NovaFlex+ införingssystem inkluderar ett handtag som tillhandahåller ett flexibelt hjul för artikulation av Flex-katetern, en avsmalnande spets vid införingssystemets distala ände för att främja korsning av den nativa klaffen, samt en ballongkateter för placering av THV. Handtaget innehåller en Flex-indikator som visar om Flex-katetern är artikulerad eller ej, ett klaffinställningshjul för finjustering av THV under klaffinställning, en tryck-/släppknapp som möjliggör rörelse mellan handtagets positioner, och en spolport för att spola Flex-katetern. En mandräng är innesluten i införingssystemets ledarlumen. Ballongkatetern har röntgentäta klaffinställningsmarkörer, som definierar klaffinställningspositionen och ballongens arbetslängd. En röntgentät dubbelmarkör, som är proximal om ballongen, indikerar Flex-kateterns position under placering.

Uppblåsningsparametrarna för placering av THV är:

Modell	Nominell ballongdiameter	Nominell uppblåsningsvolym	Angivet sprängtryck (RBP)
9355FS23	23 mm	17 ml	7 atm (709 kPa)
9355FS26	26 mm	22 ml	7 atm (709 kPa)
9355FS29	29 mm	33 ml	7 atm (709 kPa)

I följande tabell anges diametern för det ingångskärl som ska användas som ingång för införingssystemet. Ingångskärl med obstruktiv förkalkning eller signifikant tortuositet ska inte användas.

Lår-/höftkärlsdiameter	Införingssystem
≥6,0 mm	23 mm
≥6,5 mm	26 mm
≥7,0 mm	29 mm

- **Edwards sats med expanderbar införarhylsa**

Se bruksanvisningen för Edwards sats med expanderbar införarhylsa.

- **RetroFlex dilatatorsats (Figur 4)**

RetroFlex dilatatorsats innehåller en uppsättning avsmalnande dilatatorer med hydrofil beläggning för arteriell dilatation.

- **Edwards transfemoral ballongkateter**

Se Bruksanvisning för Edwards transfemoral ballongkateter.

- **Krimpverktyg (Figur 5)**

Krimpverktyget minskar THV diameter för att montera den på införingssystemet. Krimpverktyget består av en kompressionsmekanism, som stängs genom ett handtag på höljet. Krimpverktyget inkluderar ett 2-delat stopp (förpackat med införingssystemet) som används för att krimpa THV korrekt.

- **Atrion QL2530- eller QL38-anordning**

Atrion QL2530- eller QL38-anordningarna används under predilatation av nativa klaffar och placering av THV.

2.0 Indikationer

Edwards SAPIEN XT THV, NovaFlex+ leveranssystem och tillbehör indikeras hos patienter med allvarlig calcific aortastenos som kräver klaffbyte (AVR), vilken har en beräknad operations/procedur dödlighetsrisk på ≥15% utvärderat av ett riskverktyg såsom Logistic EuroSCORE eller STS-PROM.

3.0 Kontraindikationer

Användning av Edwards SAPIEN XT THV med NovaFlex+ införingssystem och tillbehör är kontraindicerad hos patienter med:

- Kongenital unicuspid eller kongenital bicuspid aortaklaff
- bevis på intracardiac massa, blodpropp, tillväxt, aktiv infektion eller endokardit
- oförmåga att tolerera antikoagulationsbehandling/ antitrombocytbehandling.

4.0 Varningar

- Instrumenten är utformade, avsedda och distribuerade endast för engångsbruk. Produkten får inte omsteriliseras eller användas på nytt. Det finns inga data till stöd för produkternas sterilitet, icke-pyrogenicitet eller funktion efter ombearbetning.
- Korrekt måttagning av THV är nödvändig för att förhindra paravalvulärt läckage, migrering och/eller annulär ruptur.
- Accelererad försämring av THV kan inträffa hos patienter med förändrad kalciummetabolism.
- Observation av pacingelektroder är nödvändig under hela proceduren för att undvika potentiell risk för perforation av pacingelektroder.
- THV måste förbli hydratiserad hela tiden och kan inte utsättas för andra lösningar än den levererade förvaringslösningen och steril fysiologisk saltlösning. THV-blad som felhanterats eller skadats under någon del av proceduren kommer att nödvändiggöra utbyte av THV.
- Patienter med tidigare existerande mitralklaffar skall undersökas noga innan THV implanteras för att säkerställa korrekt placering och isättning.
- Patienter som presenterar en kombination av lågt AV-flöde, låg lutning skall genomgå ytterligare utvärdering för att fastställa graden av aortic stenosis.
- Försiktighet skall vidtas vid implantering av THV i patienter med kliniskt viktiga kranskärlssjukdomar.
- Säkerheten vid THV implantation har inte fastställts hos patienter som har:
  - o redan existerande hjärtklaffsprotes i aortapositionen
  - o allvarlig ventrikulär dysfunktion med ejektionsfraktion <20%
  - o Hypertrofisk kardiomyopati med eller utan obstruktion
- Använd inte om THV-säkerhetsförslutningen är bruten, glutaraldehyd lösningen inte täcker THV helt, temperaturvisaren har aktiverats, THV är skadad eller om bäst före datum har gått ut.
- Misshandla inte insättningssystemet och tillbehör eller använd dem om förpackningen eller någon av komponenterna inte är steril, har öppnats eller skadats (t.ex. vikt eller utdragen), eller om bäst före datum har passerats.

5.0 Försiktighetsåtgärder

- Glutaraldehyd kan ha en irriterande effekt på hud, ögon, näsa och hals. Undvik långvarig och upprepad kontakt med eller inandning av lösningen. Får endast användas i tillräckligt ventilerade utrymmen. Vid hudkontakt ska det drabbade området genast sköljas med vatten. Vid kontakt med ögonen ska läkare omedelbart uppsökas. För ytterligare information om glutaraldehydexponering hänvisas du till vårt säkerhetsdatablad som kan erhållas från Edwards Lifesciences.
- Lämplig antibiotikaprofylax rekommenderas postoperativt för patienter som ligger i riskzonen för infektion i proteskIaffen samt endokardit.
- THV-mottagare bör stå på antikoagulant/antitrombocytbehandling, såsom fastställts av deras läkare.
- Långvarig hållbarhet har inte fastställts för THV. Regelbunden medicinsk uppföljning rekommenderas för att utvärdera klaffprestanda.

6.0 Möjliga komplikationer

Komplikationer som associeras med standard-hjärtkateterisering, ballongvalvuloplastik på aorta (BAV) och användning av anestesi innefattar men är inte begränsade till:

- Allergisk reaktion mot anestesi eller kontrastmedel, anemi, angina, arytmi, blåsljud på hjärtat, blödning, kardiovaskulär skada inklusive perforation eller dissektion av kärl, ventrikel, myokard- eller klaffstrukturer som kan kräva intervention, ledningssystemskada som eventuellt kräver en permanent pacemaker, dödsfall, embolisering inklusive luftembolisering, förkalkat klaffmaterial eller tromb, kan inte tolerera eller blir trött vid motion, femoral AV-fistel eller pseudoaneurysm, feber, hjärtsvikt, hematom, blödning som kräver transfusion eller intervention, hypertoni/ hypotoni, infektion inklusive septikemi och endokardit, inflammation, myokardinfarkt, smärta eller förändringar vid införingsplatsen, paralys, perikardiell effusion/hjärttamponad, permanent invaliditet, pleural effusion, lungödem, njursvikt, njurinsufficiens, reoperation, restenos, retroperitoneal blödning, stroke/övergående ischemiskt anfall/kluster/eller neurologiska förändringar, synkope, systemisk perifer ischemi/nervskada.

Ytterligare risker, förutom de ovan angivna, som specifikt förknippas med, men inte är begränsade till aortaklaffbyte och bioproteshjärtklaffar, är bland annat följande:

- Hjärtsvikt/låg hjärtminutvolym, hjärtstillestånd, kardiogen chock, koronarflödesobstruktion/transvalvulära flödesstörningar, försämring av anordning, explantation av anordning, embolisering av anordning, migrering eller felplacering av anordning som kräver intervention, trombos av anordning som kräver intervention, akut hjärtkirurgi, endokardit, hemolys, blödning, skada vid platsen för venös eller arteriell åtkomst som kan kräva reparation, icke akut reoperation, icke strukturell dysfunktion, paravalvulärt eller transvalvulärt läckage, potentiell koronar obstruktion p.g.a. allvarlig skrymmande förkalkning omfattande den vänstra eller högra aortaklaffspetsen, strukturell klafförsämring, (slitage, fraktur, förkalkning, bladlossning från stentpinnarna, bladretraktion, suturtråden rubbar komponenterna i en protesklaff, kordaruptur, förtjockning, stenos, eller annat); klaffregurgitation, klaffstenos, valvulär trombos; klaff implanterad på icke avsedd plats.

7.0 Bruksanvisning

7.1 Nödvändig utrustning

- Vanlig laboratorieutrustning för hjärtkateterisering
- Fluoroskopi (fasta, mobila eller halvmobila fluoroskopisystem som är lämpliga för användning vid perkutana koronarinterventioner)
- Utrustning för transesofageal eller transtorakal ekokardiografi
- Extra styv ledare med en utbyteslängd på 0,89 mm (0,035")
- Pacingledning och pacemaker (PM)
- NovaFlex+ transfemoral sats
  - Edwards SAPIEN XT THV
  - NovaFlex+ införingssystem
  - Edwards sats med expanderbar införarhylsa
  - RetroFlex dilatatorsats

  - Edwards transfemoral ballongkateter eller motsvarande
  - Krimpverktyg
  - Atrion QL2530- eller QL38-anordning (x2)
- Sterila sköljbehållare, steril fysiologisk koksaltlösning, steril hepariniserad koksaltlösning, utspädd röntgentät kontrastvätska (15:85 spädningsförhållande mellan kontrastvätska och koksaltmedium)
- Sterilt bord för förberedelse av THV och anordning
- 20 ml spruta eller större
- 50 ml spruta eller större
- Trevägskran för högt tryck (x2)

7.2 Hantering och förberedelse av THV

Använd steril teknik under förberedelse och implantation av produkten.

7.2.1 Sköljningsprocedur för THV

THV är förpackad sterilt i en plastbehållare som är tillsluten med ett skruvlock och en försegling. Innan behållaren öppnas ska den inspekteras noggrant för tecken på skada (t.ex. en sprucken behållare eller ett skadat lock, läckage, skadade eller saknade förseglingar).

Steg	Procedur
1	Ställ upp två (2) sterila skålar med minst 500 ml steril fysiologisk koksaltlösning för att noggrant skölja av glutaraldehydsteriliseringsmedlet från THV.
2	THV finns i burken inuti en hållare. Ta försiktigt ut THV-/hållaraggregatet ur behållaren utan att vidröra vävnaden. Hållaren är märkt med THV serienummer, som måste verifieras med numret på kärlets lock, och registreras i patientjournalen. Inspektera THV och leta efter tecken på skada på ramen eller vävnaden.
3	Skölj THV enligt följande: Placera THV-/hållaraggregatet i den första skålen och se till att koksaltlösningen helt täcker THV och hållaren. Med THV och hållare nedsänkt, ska THV och hållaren **försiktigt** röras om fram och tillbaka i minst 1 minut. Upprepa detta förfarande i den andra skålen i minst 1 minut. THV bör lämnas kvar i den slutliga sköljvätskan tills den ska användas, så att vävnaden inte torkar. **VAR FÖRSIKTIG: Låt inte THV komma i kontakt med sköljskålens botten eller sidor under omskakning eller omrörning av denna. Försiktighet måste vidtas för att säkerställa att identifikations-etiketten inte kommer i kontakt med och skadar vävnaden. Inga andra föremål får placeras i sköljskålarna.**

7.2.2 Förbered systemet

Steg	Procedur
1	Inspektera alla komponenter visuellt och leta efter skador. Säkerställ att NovaFlex+ införingssystem är helt utan krökar och att klaffinställningshjulet och handtaget sitter i nivå med varandra.
2	Fyll och spola ledarlumen på införarhylsan och dilatatorerna med hepariniserad koksaltlösning. Spola igenom spolporten på införarhylsan och införingssystemet. Hydratisera dilatatorerna och införaren längs hela deras längd.
3	Avlägsna försiktigt det distala ballongskyddet från införingssystemet. Placera införingssystemet i standardposition och kontrollera att Flex-kateterns spets är täckt av det proximala ballongskyddet.
4	Skruva laddarlocket av laddaren och spola laddarlocket med hepariniserad koksaltlösning.
5	Placera laddarlocket på införingssystemet med lockets insida vänt mot den distala änden. För ut införingssystemet ur standardpositionen och för det tillbaka till förpackningsposition med anordningens handtag intill Y-kopplingen. Dra försiktigt av det proximala ballongskyddet över den blå delen av ballongskaftet.
6	Anslut en trevägskran till ballonguppblåsningsporten. Fyll en 50 ml eller större spruta med 10–20 ml utspätt kontrastmedel och anslut trevägskranen.
7	Fyll lämplig Atrion-anordning med större volym än den indikerade uppblåsningsvolymen. Lås och anslut till trevägskranen.
8	Använd 50 ml-sprutan eller en större spruta för att dra ur luft och skapa vakuum. Upprepa tills alla luftbubblor har avlägsnats från systemet. Släpp kolven sakta för att tillförsäkra att kontrastmedlet kommer in i införingssystemets lumen. Lämna trycket nollställt i systemet.
9	Med knappen på Atrion-anordningen avlägsnas kontrastmedel inne i sprutan för att uppnå den volym som krävs för att placera THV, enligt följande: **Införingssystem** / **THV** / **Uppblåsningsvolym** Modell 9355FS23 / 23 mm / 17 ml Modell 9355FS26 / 26 mm / 22 ml Modell 9355FS29 / 29 mm / 33 ml
10	Verifiera att uppblåsningsvolymen är korrekt, efter att trevägskranen öppnats. **VAR FÖRSIKTIG: Bibehåll Atrion-anordningen i den låsta positionen tills THV ska placeras.**

7.2.3 Montera och krimpa THV på införingssystemet

Steg	Procedur
1	Ställ upp två (2) sterila skålar med minst 100 ml steril fysiologisk koksaltlösning för att noggrant skölja av Qualcrimp krimptillbehör.
2	Sänk ned Qualcrimp krimptillbehör helt i den första skålen och tryck försiktigt ihop det för att tillförsäkra att all saltlösning absorberats. Rör långsamt om Qualcrimp krimptillbehöret i minst 1 minut. Upprepa detta förfarande i den andra skålen.

Steg	Procedur
3	Ta ut THV ur hållaren och avlägsna ID-etiketten.
4	Koppla den tvådelade krimpstoppern till krimpverktygets bas och snäpp den på plats.
5	Starta med krimpverktyget i den öppna positionen och krimpa gradvis THV till en diameter på ca 21 mm tills den passar inuti Qualcrimp krimptillbehöret.
6	Placera Qualcrimp krimptillbehör över THV och orientera Qualcrimp krimptillbehörets skört mot inflödet (tygmanschettens ände) på THV.
7	Placera försiktigt THV och Qualcrimp i krimpverktygets öppning. För in införingssystemet koaxialt inuti bioprotesen i klaffkrimpdelen av införingssystemet (Figur 3a – 2–3 mm distalt om det blå ballongskaftet) med bioprotesens inflöde vänt mot införingssystemets distala ände.
8	Centrera ballongskaftet centralt inuti klaffen. Krimpa THV tills den når Qualcrimp-stoppet.
9	Avlägsna försiktigt Qualcrimp krimptillbehör från THV och Qualcrimp-stopp från krimpverktygets stopper, och lämna slutstoppet på plats.
10	Krimpa THV fullständigt tills den når slutstoppet. **OBS! Säkerställ att klaffkrimpdelen (Figur 3a) är koaxial inuti THV.**
11	Upprepa den fullständiga krimpningen av THV.
12	Dra ballongskaftet tills det låses i standardpositionen.
13	Spola laddaren med hepariniserad koksaltlösning. För omedelbart fram THV i laddaren tills införingssystemets avsmalnande spets sticker ut. **VAR FÖRSIKTIG: För att förhindra eventuell skada på bladen, bör THV inte förbli helt krimpad och/eller vara kvar i laddaren i mer än 15 minuter.**
14	Skruva på locket på laddaren och spola Flex-katetern igen. Avlägsna mandrängen och spola införingssystemets ledarlumen. **VAR FÖRSIKTIG: Läkaren måste verifiera att THV är korrekt inriktad innan den implanteras; inflödet (tygmanschettänden) på THV bör vara inriktad distalt mot den avsmalnande spetsen.**

7.3 Fördilatation av nativ klaff och THV-införande

Fördilatation av nativ klaff och införing av klaffprotes bör utföras under lokal och/eller allmän anestesi med hemodynamisk övervakning i ett kombinerat kateteriseringslab/operationsrum med fluoroskopisk och ekokardiografisk bildkapacitet.

Applicera heparin för att bibehålla ACT vid ≥250 sek.

7.3.1 Basparametrar

Steg	Procedur
1	Utför ett supra-aortaangiogram med projektionen av den nativa aortaklaffen vinkelrätt mot bilden.
2	Bedöm avståndet mellan den vänstra och högra kranskärlsostia från aortic annulus i relation till THV ramhöjd.
3	För in en pacemaker- (PM) elektrod tills dess distala ände är positionerad i den högra kammaren.
4	Ställ in stimuleringsparametrarna och testa pacing.

7.3.2 Fördilatation av nativ klaff

Se Bruksanvisning för Edwards transfemoral ballongkateter.

VAR FÖRSIKTIG: Implantation av klaffprotes bör inte utföras om ballongen inte kan blåsas upp helt under fördilatationen.

7.3.3 Införande av THV

Steg	Procedur
1	Fördilatera lår-/höftkärlet med användning av RetroFlex dilatatorsats, genom att föra fram dilatatorer av ökande storlek över ledaren tills lämplig diameter uppnåtts. För fram så mycket av dilatatorns längd som möjligt över ledaren medan du följer dess förflyttning framåt med fluoroskopi.
2	Förbered och för in införarhylsan enligt bruksanvisningen.
3	För in laddaraggregatet i införarhylsan tills laddaren stannar.
4	För fram NovaFlex+ införingssystem med Edwards logotyp vänd uppåt genom införarhylsan tills THV kommer ut ur hylsan. **OBS! Bibehåll korrekt orientering för Flex-katetern (med Edwards logotyp vänd uppåt) genom hela proceduren.** **VAR FÖRSIKTIG: THV bör inte föras genom införarhylsan om hylsans spets inte har passerat aortabifurkationen.** **VAR FÖRSIKTIG: För att förebygga eventuella skador på klaffbladen skall inte THV vara kvar i införarhylsan under mer än 2 minuter.**
5	Initiera klaffinställning i en rak del av aorta descendens genom att trycka på knappen Press/Release (Tryck/Släpp), dra tillbaka ballongkatetern och släppa upp knappen. Fortsätt dra tillbaka ballongkatetern tills införingssystemet låses i klaffinställningsposition (Se **Figur 3c**). Använd klaffinställningshjulet för att centrera THV mellan klaffinställningmarkörerna. **OBS! Vrid inte klaffinställningshjulet om införingssystemet inte är låst i klaffinställningspositionen.** **VARNING: Positionera inte THV bortom den distala klaffinställningsmarkören. Detta förhindrar korrekt placering av klaffen.** **VAR FÖRSIKTIG: Bibehåll ledarens position i den vänstra kammaren under klaffinställning.**
6	Använd flexhjulet för att svänga i aortabågen och korsa den nativa klaffen. **OBS! Verifiera att Edwards logotyp är vänd uppåt. Införingssystemet artikulerar i motsatt riktning från spolporten.**

Steg	Procedur
7	Om ytterligare arbetslängd behövs ska laddaren avlägsnas genom att skruva av laddarens lock och skala av laddarens slangar från införingssystemet.
8	Dra tillbaka Flex-katetern till den dubbla markören och placera THV.
9	Verifiera att THV är i korrekt position i förhållande till den nativa klaffen.
10	Se till att klaffen är korrekt inriktad mellan markörerna.
11	Påbörja placering av THV: • Lås upp Atrion-anordningen. • Kontrollera att hemodynamisk stabilitet är etablerad och påbörja snabbt pacing; när det arteriella blodtrycket har sjunkit till 50 mmHg eller lägre, kan ballonguppblåsningen påbörjas. • Placera THV genom att blåsa upp ballongen med hela volymen i Atrion-anordningen, håll kvar i 3 sekunder och kontrollera att Atrion-anordningens cylinder är tom för att säkerställa fullständig uppblåsning av ballongen. • Töm ballongen. Stäng av pacemakern när ballongkatetern har tömts helt.

7.3.4 Systemborttagning

Steg	Procedur
1	Räta ut införingssystemet vid passering av aortabågen. Dra tillbaka Flex-katetern tills den låses på plats i standardposition och ta bort den från hylsan. **VAR FÖRSIKTIG: Patienten kan skadas om införingssystemet inte är avartikulerat före avlägsnande.**

7.4 Verifiering av klaffposition och mätningar

Mät och registrera hemodynamiska parametrar.

Steg	Procedur
1	Utför ett angiogram över aorta för att utvärdera klaffens funktion och koronaröppenheten.
2	Mät och registrera de transvalvulära tryckgradienterna.
3	Avlägsna alla anordningar när ACT-nivån är lämplig (t.ex. når <150 sek.). Se bruksanvisningen för införarhylsan om hur anordningen ska avlägsnas.
4	Slut införingsplatsen.

8.0 Leverans

THV levereras sterilt och icke-pyrogent förpackad i buffrad glutaraldehyd, i en plastbehållare till vilken en manipulationssäker försegling har applicerats. Varje behållare transporteras i en förvaringslåda med en temperaturindikator för att detektera om THV exponeras för extrema temperaturer. Förvaringslådan packas sedan in i frigolit före transporten.

Införingssystemet och tillbehören levereras påsförpackade och är steriliserade med etylenoxid. Atrion QL2530- och QL38-anordningarna levereras i en termoformad, avskalningsbar bricka och är steriliserade med etylenoxid.

8.1 Förvaring

THV måste förvaras vid 10°C–25°C (50°F–77°F). Införingssystemet och dess tillbehör ska förvaras svalt och torrt.

9.0 MRT-säkerhet

MR **MR-säker**

Icke-kliniska tester hat visat att THV (implantat) är MRT-villkorlig. Den kan skannas utan risk vid följande förhållanden:

- Statiskt magnetfält på 1,5 Tesla (T) eller 3,0 Tesla (T).
- Spatialgradientfält på 2500 gauss/cm eller mindre.
- Maximal medeluppsugningshastighet för hel kropp (WB-SAR) av 2,0 W/kg under 15 minuters skanning.
- Normal lägesoperation, enligt definition i IEC 60601-2-33, Ed. 2.0, för MR-system.

I icke-kliniska tester och analyser, fastställdes att implantatet producerade en *in vivo* temperaturhöjning på mindre än 1,3°C över bakgrunden för en WB-SAR på 2,0 W/kg under 15 minuters MR-skanning i ett 1,5 T GE Signa cylindriskt helkropps MRT-system. Den projekterade *in vivo*-höjningen över bakgrunden var 1,5°C för en WB-SAR på 2,0 W/kg i ett 3,0 T GE Signa HDxt 3T cylindriskt helkropps MR-system. Dessa beräkningar övervärderar den verkliga *in vivo* -ökningen, eftersom man inte tar hänsyn till blodets kylningseffekt.

Bildartefakten utökas så långt som 10 mm från implantatet för roterande ekobilder och 30 mm för gradienta ekobilder när de skannades i en icke klinisk test med ett 3,0 T GE Signa HDx MR-system.

Implantatet har inte utvärderats i MR-system annat än 1,5 T eller 3,0 T.

10.0 Patientinformation

Ett patientregistreringsformulär levereras med varje THV. Fyll i alla begärda uppgifter efter implantationen. Serienumret återfinns på förpackningen och på ID-etiketten som sitter på THV. Skicka formuläret till den Edward Lifesciences-adress som finns angiven på formuläret och ge det tillfälliga id-kortet till patienten innan han eller hon skrivs ut.

11.0 Återvunna THV och avyttring av anordningar

En explanterad THV bör placeras i ett lämpligt histologiskt fixativ, t.ex. 10% formalin eller 2% glutaraldehyd, och returneras till företaget. Nedkylning behövs inte under dessa förhållanden. Kontakta Edwards Lifesciences för att beställa en explantationssats.

Använda instrument kan hanteras och kasseras på samma sätt som sjukhusavfall och bioriskmaterial. Det finns inga speciella risker förknippade med avyttring av dessa instrument.

Dessa produkter är tillverkade och säljs under ett eller flera av följande amerikanska patent: Amerikanska patentnummer 5,411,552; 5,931,969; 6,210,957; 6,214,054; 6,547,827; 6,561,970; 6,893,460; 6,908,481; 7,214,344; 7,510,575; 7,530,253; 7,585,321; 7,780,723; och RE40570 och motsvarande utländska patent. Ytterligare patent sökta.

Dansk

Brugsanvisning

Implantation af transkateterhjerteklappen skal udføres af læger, der er blevet oplært af Edwards Lifesciences. Den implanterende læge bør have erfaring med ballonvalvuloplastik på aorta.

Produktnavn	23 mm system	26 mm system	29 mm system
	Model/REF		
NovaFlex+ transfemoralsættet består af følgende:			
Edwards SAPIEN XT transkateterhjerteklap	9300TFX (23 mm)	9300TFX (26 mm)	9300TFX (29 mm)
NovaFlex+ fremføringssystem[1]	9355FS23	9355FS26	9355FS29
Edwards udvidelige indføringshylster	916ES23	918ES26	920ES29
RetroFlex dilatatorsæt	9100DKS		
Edwards transfemoralt ballonkateter	9350BC20	9350BC23	9350BC25
Kompressionsanordning	9350CR		
Atrion QL2530 oppumpningsanordning	96402		
Atrion QL38 anordning med låsende kanyle			96406
[1] Qualcrimp kompressionstilbehør, 9300QC og en 2-delt kompressionsstopper medfølger			

1.0 Instrumentbeskrivelse

- **Edwards SAPIEN XT transkateterhjerteklap (Figur 1)**

Edwards SAPIEN XT transkateterhjerteklap (THV eller bioprotese) består af en ballonekspanderbar, røntgenfast, kobolt-krom-ramme, en trebladet bovin perikardieklap og polyethylenterephthalat (PET)-stof. Den er behandlet i overensstemmelse med Edwards ThermaFix proces og er emballeret og endeligt steriliseret i glutaraldehyd.

THV er beregnet til at implantation i et nativt annulusstørrelsesinterval, der kan sammenlignes med følgende transøsofageale ekkokardiografi (TEE)-målinger:

Nativt klapannulusstørrelse	Bioprotesestørrelse
18–22 mm	23 mm
21–25 mm	26 mm
24–27 mm	29 mm

- **Qualcrimp kompressionstilbehør (Figur 2)**

Qualcrimp kompressionstilbehøret (følger med NovaFlex+ fremføringssystemet) bruges under kompression af THV.

- **NovaFlex+ fremføringssystem (Figur 3a, 3b, 3c)**

NovaFlex+ fremføringssystemet indeholder et håndtag med et Flex-hjul til bøjning af Flex-katetret, en konisk spids i fremføringssystemets distale ende til at muliggøre krydsning af den native ventil og et ballonkateter til indsættelse af THV'en. Håndtaget har en Flex-indikator, der viser, om Flex-katetret er bøjet, et klapjusteringshjul til finjustering af THV'en under klapjustering, en tryk-/udløserknap, der muliggør bevægelse mellem håndtagets positioner og en udskylningsport til udskylning af Flex-katetret. Der er en stilet inde i guidewirelumen på fremføringssystemet. Ballonkatetret har røntgenfaste klapjusteringsmarkører, der angiver klapjusteringspositionen og ballonens arbejdslængde. En røntgenfast dobbeltmarkør proksimal til ballonen angiver Flex-katetrets position under indsættelse.

Oppumpningsparametrene for indsættelse af THV er:

Model	Nominel ballondiameter	Nominel oppumpnings-volumen	Bedømt sprængningstryk (BST)
9355FS23	23 mm	17 ml	7 atm (709 kPa)
9355FS26	26 mm	22 ml	7 atm (709 kPa)
9355FS29	29 mm	33 ml	7 atm (709 kPa)

Følgende tabel identificerer diametrene af adgangsblodkar, der bør benyttes som adgang for fremføringssystemet. Adgangsblodkar bør være uden alvorlige obstruerende kalkdannelser eller alvorlige snoninger.

Diameter af iliofemoralt blodkar	Fremføringssystem
≥6,0 mm	23 mm
≥6,5 mm	26 mm
≥7,0 mm	29 mm

- **Edwards udvidelige indføringshylster**

Se brugsanvisningen for Edwards udvidelige indføringshylster.

- **RetroFlex dilatatorsæt (Figur 4)**

RetroFlex dilatatorsættet indeholder et sæt hydrofilt belagte tilspidsede dilatatorer, der bruges til arteriedilatation.

- **Edwards transfemoralt ballonkateter**

Der henvises til betjeningsvejledningen for Edwards transfemorale ballonkateter.

- **Kompressionsanordning (Figur 5)**

Kompressionsanordningen mindsker THV'ens diameter, så den kan påsættes fremføringssystemet. Kompressionsanordningen består af en kompressionsmekanisme, der lukkes ved hjælp af et håndtag på kabinettet. Kompressionsanordningen har en 2-delt stopper (medfølger fremføringssystemet), der anvendes til korrekt kompression af THV'en.

- **Atrion QL2530 eller QL38 anordning**

Atrion QL2530 eller QL38 anordningerne bruges under nativ klapprædilatation og THV-implementering.

2.0 Indikationer

Edwards SAPIEN XT THV, NovaFlex+ leveringssystemet og tilbehør er indiceret til brug hos patienter med symptomatisk svært forkalket aorta stenose, der kræver aortaklappen udskiftet (Aortic Valve Replacement = AVR), og som har en anslået operativ/proceduremæssig risiko for dødsfald på op til 15% vurderet iht. risikomodeller som Logistic EuroSCORE eller STS-PROM.

3.0 Kontraindikationer

Brugen af Edwards SAPIEN XT THV sammen med NovaFlex+ fremføringssystem og tilbehør er kontraindikeret hos patienter med:

- Medfødt unikuspid eller medfødt bikuspid aortaklap,
- Bevis for intrakardiel masse, trombe, vegetation, aktiv infektion eller endocarditis,
- manglende evne til at tåle antikoagulationsbehandling.

4.0 Advarsler

- Anordningerne er kun designet, beregnet og distribueret til engangsbrug. Anordningerne må ikke resteriliseres eller genanvendes. Der er ingen data, som understøtter, at anordningerne er sterile, ikke-pyrogene og funktionelle efter genforarbejdning.
- Fejlagtig dimensionering af THV'en kan føre til paravalvulær lækage, vandring og/eller ringformet ruptur.
- Accelereret forringelse af THV'en kan forekomme hos patienter med forandret calciummetabolisme.
- Observation af paceledningen er afgørende under hele proceduren, så den potentielle risiko for perforation af paceledningen undgås.
- THV'en skal forblive hydreret på alle tidspunkter og må ikke udsættes for andre løsninger end sin lagringsløsning og sterile fysiologiske saltvandsopløsning. THV'ens foldere, som er blevet mishandlet eller beskadiget under proceduren, vil kræve udskiftning af THV'en.
- Patienter med præ-eksisterende mitralklapudstyr, bør vurderes nøje, inden implantation af THV for at sikre en korrekt THV positionering og implementering.
- Patienter med kombination AV lavt flow, lav gradient bør underkastes yderligere evaluering for at fastslå graden af aorta stenose.
- Der bør udvises forsigtighed i implantering af en THV hos patienter med klinisk signifikante koronararteriesygdomme.
- Sikkerheden af THV implantationen er ikke påvist hos patienter, der har:
  - o Præ-eksisterende protetisk hjerteklap i den aortiske position
  - o Svær ventrikulær dysfunktion med ejektionsfraktion <20%
  - o Obstruktiv eller non-obstruktiv hypertrofisk kardiomyopati
- Brug ikke THV'en, hvis forseglingen er brudt, lækker, glutaraldehyd lagringsløsningen ikke fuldstændigt dækker THV'en, temperaturindikatoren er blevet aktiveret, THV'en er beskadiget, eller udløbsdatoen er overskredet.
- Misbrug ikke leveringssystemet og tilbehør, og brug dem ikke, hvis emballagen eller komponenter ikke er sterile, er blevet åbnet eller beskadiget (f.eks bøjet eller strakt), eller udløbsdatoen er overskredet.

5.0 Forholdsregler

- Glutaraldehyd kan forårsage irritation af huden, øjnene, næsen og halsen. Undgå længerevarende eller gentagen udsættelse for eller indånding af opløsningen. Bør kun bruges med ordentlig udluftning. Hvis der opstår kontakt med huden, skal det berørte område straks skylles med vand. I tilfælde af kontakt med øjnene skal der straks søges læge. For mere information om glutaraldehydeksponering henvises der til Sikkerhedsdatabladet, der fås fra Edwards Lifesciences.
- Der anbefales passende antibiotisk profylakse hos patienter med risiko for infektion af den protetiske ventil og endocarditis.
- THV-modtagere bør fortsætte med antikoagulerende behandling som fastlagt af deres læge.
- Der er ikke fastlagt nogen langtidsholdbarhed for THV'en. Der tilrådes regelmæssig lægelig opfølgning for at evaluere ventilens præstation.

6.0 Potentielle bivirkninger

Komplikationer forbundet med standard kardial kateterisation, ballonvalvuloplastik (BAV) og brug af anæstesi omfatter, men er ikke begrænset til:

- Unormale laboratorieværdier, allergisk reaktion over for anæstesi eller over for kontrastmedier, anæmi (inkl. hæmolytisk anæmi), angina, arytmi, hjertemislyd, blødning, kardiovaskulære skader som f.eks. perforation eller dissektion af blodkar, ventrikulære, myokardie- eller valvulære strukturer, der kan behøve intervention, ledningssystemsskade, som kan behøve en permanent pacemaker, dødsfald, embolisation herunder luft, forkalket ventilmateriale eller trombe, motionsintolerans eller svaghed, femoral AV-fistel eller pseudoaneurisme, feber, hjertesvigt, hæmatom, blødning, der kræver transfusion eller intervention, hypertension/hypotension, infektion, der omfatter sepsis og endocarditis, betændelse, myokardie-infarkt, smerte eller ændringer på adgangsområdet, lammelse, perikardiel effusion/hjertetamponering, permanent invaliditet, pleural effusion, pulmonært ødem, nyresvigt, nyreinsufficiens, genoperation, restenose, retroperitonæal blødning, slagtilfælde/kortvarig iskæmisk anfald/eller neurologiske forandringer, synkope, systemisk perifer iskæmi-/nerveskade.

Ud over de ovenfor anførte risici ovenfor omfatter yderligere mulige risici specifikt forbundet med aortaklapudskiftning og bioprotetiske hjerteklapper, men er muligvis ikke begrænset til følgende:

- Hjertesvigt/lav minutvolumen, hjertestop, kredsløbstilstand, koronarflowobstruktion/transvalvulær flowforstyrrelser, anordningsdegeneration, anordningseksplantation, anordningsembolisation, anordningsvandring eller fejlplacering, der kræver intervention, anordningstrombose, der kræver intervention, nødhjerteoperation, hæmolyse, blødning, beskadigelse af stedet for vene- eller arterieadgang, der kan behøve reparation, ikke-opdukkende genoperation, ikke-strukturel dysfunktion, paravalvulær eller transvalvulær lækage, potentiel koronarobstruktion som følge af alvorlig massiv forkalkning, der omfatter aortaklappens venstre eller højre spidser, strukturel klapforringelse (slitage, fraktur, forkalkning, bladflænge/brist fra stentposten, bladtilbagetrækning, suturlinjeforstyrrelse af en protetisk klaps komponenter, chordal ruptur, fortykkelse, stenose eller andet), klapregurgitation, klapstenose, valvulær trombose, klap implanteret på et ikke-planlagt sted.

7.0 Brugsanvisning

7.1 Påkrævet udstyr

- Standard laboratorieudstyr til hjertekateterisation
- Fluoroskopi (faste, mobile eller semi-mobile fluoroskopisystemer, der er velegnede til brug i forbindelse med perkutane koronarinterventioner)
- Transøsofageale og transtorakale ekkokardiografimuligheder
- Udskiftningsguidewire, længde 0,89 mm (0,035"), ekstra stiv
- Pacemaker (PM) og paceledning
- NovaFlex+ transfemoralsæt
  - Edwards SAPIEN XT THV
  - NovaFlex+ fremføringssystem

- Edwards udvidelige indføringshylster
- RetroFlex dilatatorsæt
- Edwards transfemoralt ballonkateter eller tilsvarende
- Kompressionsanordning
- Atrion QL2530 eller QL38 anordning (x2)

- Sterile skyllebeholdere, steril fysiologisk saltvandsopløsning, steril hepariniseret saltvandsopløsning og fortyndet røntgenfast kontrastmiddel (15:85 middel til saltvandsfortynding)
- Sterilt bord til THV- og anordningsklargøring
- 20 ml injektionssprøjte eller større
- 50 ml injektionssprøjte eller større
- Tredelt højtryksstophane (x2)

7.2 Håndtering og klargøring af THV

Følg steril teknik under klargøring og implantation af instrumentet.

7.2.1 THV-rensningsprocedure

THV'en er pakket sterilt i en plastikkrukke med en lukning med skruelåg og forsegling. Før den åbnes, skal beholderen undersøges grundigt for tegn på beskadigelse (f.eks. revner i beholderen eller låget, lækage eller defekte eller manglende forseglinger).

Trin	Procedure
1	Klargør to (2) sterile skåle med mindst 500 ml sterilt fysiologisk saltvand for at skylle glutaraldehyd-sterilanten fra THV'en omhyggeligt.
2	THV'en ligger i krukken i en holder. THV-/holdersamlingen tages forsigtigt ud af krukken uden at røre ved vævet. Holderen er mærket med THV-serieidentifikationsnummeret, som skal bekræftes med nummeret på krukkens låg og anføres i patientinformationsdokumenterne. Efterse THV'en for tegn på skader på rammen eller klappens væv.
3	Skyl THV'en som følger: Anbring THV-/holdersamlingen i den første skål og sørg for, at saltvandsopløsningen dækker THV'en og holderen helt. Mens THV'en og holderen er nedsænket, skal du **forsigtigt** skvulpe THV'en og holderen frem og tilbage i et minut. Gentag denne proces i den anden skål i mindst 1 minut. THV'en efterlades i den sidste skylleopløsning, indtil den skal bruges, for at forhindre vævet i at tørre. **FORSIGTIG: Lad ikke THV'en komme i kontakt med bunden eller siderne af skylleskålen under vippen eller skvulpen. Der skal udvises forsigtighed for at sikre, at identifikationsmærket ikke kommer i kontakt med og skader vævet. Der må ikke anbringes andre objekter i skylleskålene.**

7.2.2 Klargør systemet

Trin	Procedure
1	Efterse visuelt alle komponenter for beskadigelse. Sørg for, at NovaFlex+-fremføringssystemet er helt foldet ud og at klapjusteringshjulet er på niveau med håndtaget.
2	Klargør og skyl guidewirelumen på introduceren og dilatatorerne med hepariniseret saltvand. Skyl igennem via indføringshylstrets og fremføringssystemets udskylningsport. Aftør hele længden af dilatatorerne og introduceren.
3	Fjern forsigtigt den distale ballons emballage fra fremføringssystemet. Anbring fremføringssystemet i default-positionen og sørg for, at flexkateterets spids er dækket af emballagen på den proksimale ballon.
4	Tag låget af indsætningsanordningen og skyl låget med hepariniseret saltvand.
5	Anbring låget fra indsætningsanordningen på fremføringssystemet med det indvendige af låget vendt mod den distale spids. Tag fremføringssystemet ud af default-positionen og tilbage til emballerede position, hvor systemets håndtag befinder sig ved siden af Y-konnektoren. Træk forsigtigt emballagen på den proksimale ballon af over den blå del på ballonskaftet.
6	Fastgør en tredelt stophane på ballonens oppumpningsport. Fyld en 50 ml injektionssprøjte eller større med 10–20 ml fortyndet kontrastmiddel, og fastgør den til den tredelte stophane.
7	Fyld den passende Atrion anordning med overskydende luft svarende til den angivne oppumpningsvolumen. Lås og fastgør den 3-delte stophane.
8	Træk vakuum med en 50 ml injektionssprøjte eller større for at fjerne luft. Gentag, indtil alle luftbobler er fjernet fra systemet. Giv langsomt slip på stemplet for at sikre, at kontrastmidlet trænger ind i lumen på fremføringssystemet. Lad der være et nultryk i systemet.
9	Fjern kontrastmidlet med knappen på Atrion anordningen til injektionssprøjten for at nå den rette volumen, der påkræves til isættelse af THV'en, i henhold til følgende: <table><tr><th>Fremføringssystem</th><th>THV</th><th>Oppumpningsvolumen</th></tr><tr><td>Model 9355FS23</td><td>23 mm</td><td>17 ml</td></tr><tr><td>Model 9355FS26</td><td>26 mm</td><td>22 ml</td></tr><tr><td>Model 9355FS29</td><td>29 mm</td><td>33 ml</td></tr></table>
10	Efter åbning af stophanen skal det bekræftes, at oppumpningsvolumen er korrekt. **FORSIGTIG: Atrion anordningen skal være i låst position indtil indsættelse af THV.**

7.2.3 Fastgør og komprimer THV'en på fremføringssystemet

Trin	Procedure
1	Klargør to (2) sterile skåle med mindst 100 ml sterilt fysiologisk saltvand til grundig skylning af Qualcrimp kompressionstilbehøret.
2	Nedsænk Qualcrimp kompressionstilbehøret helt i den første skål, og komprimer det forsigtigt for at sikre fuldstændig saltvandsabsorbering. Skvulp langsomt Qualcrimp kompressionstilbehøret i mindst 1 minut. Gentag denne proces i den anden skål.
3	Fjern THV'en fra holderen og fjern ID-mærket.
4	Påsæt den todelte kompressionsstopper på den nederste del af kompressionsanordningen og klik den på plads.
5	Med kompressionsanordningen i åben position til at begynde med skal THV'en gradvist komprimeres til en diameter på cirka 21 mm, indtil den passer ind i Qualcrimp kompressionstilbehøret.
6	Anbring Qualcrimp kompressionstilbehøret over THV'en, mens Qualcrimp kompressionstilbehørets skørt vendes mod indløbssiden (tekstilmanchetenden) på THV'en.
7	Anbring forsigtigt THV'en og Qualcrimp i kompressionsåbningen. Indfør fremføringssystemet koaksialt inde i THV'en i klapkompressionssektionen på fremføringssystemet (Figur 3a – 2–3 mm distalt for det blå ballonaksel) med THV'ens indløbsside mod den distale ende på fremføringssystemet.
8	Centrér ballonakslet koaksialt inde i klappen. Komprimér THV'en indtil den når Qualcrimp-stopperen.
9	Fjern forsigtigt Qualcrimp kompressionsanordningen fra THV'en og Qualcrimp stopperen fra den 2-delte kompressionsstopper. Lad den sidste stopper sidde.
10	Komprimér THV'en helt indtil den når den sidste stopper. **BEMÆRK: Sørg for, at klapkompressionssektionen (Figur 3a) er koaksial inde i THV'en.**
11	Gentag fuld kompression af THV'en.
12	Træk i ballonskaftet, indtil det fastlåses i Default-positionen.
13	Skyl indsætningsanordningen med hepariniseret saltvand. Før øjeblikkeligt THV'en ind i indsætninganordningen, indtil fremføringssystemets koniske spids blotlægges. **FORSIGTIG: For at forhindre eventuel bladbeskadigelse bør THV'en ikke forblive fuldt komprimeret og/eller i indsætningsanordningen i mere end 15 minutter.**
14	Skru indsætningsanordningens låg på indsætningsanordningen, og skyl Flex-kateteret igen. Fjern stiletten og skyl fremføringssystemets guidewirelumen. **FORSIGTIG: Lægen skal kontrollere, at THV'en vender rigtigt forud for dens implantation. Indløbssiden (tekstilmanchetenden) på THV'en bør vende distalt mod den koniske spids.**

7.3 Nativ ventilpredilatation og THV-fremføring

Predilatation af den native klap og fremføring af proteseklappen bør udføres under lokal eller generel anæstesi med hæmodynamisk overvågning i et kateterisationslaboratorium/en hybrid operationsstue med mulighed for fluoroskopisk og ekkokardiografisk billeddannelse.

Giv heparin for at fastholde ACT ved ≥250 sek.

7.3.1 Baselineparametre

Trin	Procedure
1	Udfør et supraaortisk angiogram med projektionen af den native aortaklap vinkelret på visningen.
2	Vurder afstanden på venstre og højre koronarudmunding fra aorta annulus i forhold til rammehøjden på THV'en.
3	Før en pacemakerledning ind, til dens distale ende befinder sig i højre ventrikel.
4	Indstil stimulationsparametrene og test pacing.

7.3.2 Nativ ventilpredilation

Der henvises til betjeningsvejledningen for Edwards transfemorale ballonkateter.

FORSIGTIG: Implantation af proteseklap bør ikke udføres, hvis ballonen ikke kan pumpes helt op under predilatationen.

7.3.3 Fremføring af THV

Trin	Procedure
1	Femoro-iliakalkarret predilateres ved hjælp af RetroFlex-dilatatorsættet ved at føre dilatatorer i stigende størrelse frem over guidewiren, indtil den passende diameter nås. Fremfør dilatatoren så langt som muligt over guidewiren, mens fremføringen følges på fluoroskopi.
2	Indføringshylstret forberedes og indføres som beskrevet i brugsanvisningen.
3	Før indsætningsanordningssættet ind i NovaFlex-indføringshylstret, indtil indsætningsanordningen stopper.
4	Før NovaFlex+ fremføringssystemet med Edwards-logoet vendende opad gennem NovaFlex-indføringshylstret, indtil THV'en forlader hylstret. **BEMÆRK: Oprethold korrekt retning på flex-katetret (med Edwards-logoet vendende opad) under hele indgrebet.** **FORSIGTIG: THV'en bør ikke føres frem gennem NovaFlex-indføringshylstret, hvis ikke hylsterspidsen har passeret den aortiske tvedeling.** **FORSIGTIG: For at forhindre eventuelle folder og skader bør THV ikke forblive i loaderen i mere end 2 minutter.**

Trin	Procedure
5	Justering af klappen påbegyndes på en lige del af aorta decendens ved at trykke på tryk-/udløserknappen, mens ballonkatetret trækkes tilbage og knappen slippes. Fortsæt med at trække ballonkatetret helt tilbage indtil fremføringssystemet låses i klapjusteringspositionen (Se **Figur 3c**). Anvend klapjusteringshjulet til at centrere THV'en mellem klapjusteringsmarkørerne. **BEMÆRK: Klapjusteringshjulet må ikke drejes, hvis ikke fremføringssystemet er fastlåst i klapjusteringspositionen.** **ADVARSEL: THV'en må ikke placeres efter den distale klapjusteringsmarkør. Dette vil forhindre korrekt klapindsættelse.** **FORSIGTIG: Oprethold ledetrådens placering i den venstre ventrikel under klapjustering.**
6	Anvend Flex-hjulet til at gennemkrydse arcus aortae og krydse den native klap. **BEMÆRK: Kontrollér at Edwards-logoet vender opad. Fremføringssystemet artikulerer i en modsat retning af udskylningsporten.**
7	Hvis der er behov for yderligere arbejdslængde, fjernes indsætningsanordningen ved at skrue indsætningsanordningens låg af og fjerne indsætningsanordningsslangen på fremføringssystemet.
8	Træk Flex-katetret tilbage til dobbeltmarkøren og anbring THV'en.
9	Kontrollér at THV er i korrekt position i forhold til den native klap.
10	Sørg for, at klappen er korrekt justeret mellem markørerne.
11	Påbegynd indsættelse af THV: • Lås Atrion anordningen op. • Sørg for, at der er hæmodynamisk stabilitet og påbegynd hurtig pacing; når det arterielle blodtryk er faldet til 50 mmHg eller under, kan ballonoppumpning påbegyndes. • Indsæt THV'en ved at puste ballonen op med hele mængden indeholdt i Atrion anordningen, hold den i 3 sekunder og bekræft, at Atrion anordningens kammer er tomt for at sikre, at ballonen er fuldstændigt oppustet. • Luk luften ud af ballonen. Når ballonkateteret er helt klappet sammen, slukkes for pacemakeren.

7.3.4 Fjernelse af system

Trin	Procedure
1	Fold fremføringssystemet ud mens arcus aortae gennemkrydses. Træk Flex-katetret tilbage, indtil det fastlåses i Default-positionen og fjern det fra hylstret. **FORSIGTIG: Der kan forekomme patientskade, hvis ikke fremføringssystemet rettes ud inden fjernelse.**

7.4 Bekræftelse af den protetiske klaps placering og mål

Mål og registrer de hæmodynamiske parametre.

Trin	Procedure
1	Udfør supraaortisk angiografi for at bedømme anordningens ydelse og koronare åbenhed.
2	Mål og nedskriv de transvalvulære trykgradienter.
3	Fjern alle anordninger, når ACT-niveauet er passende (f.eks. når <150 sek.). Se brugsanvisningen for indføringshylstret mht. fjernelse af instrumentet.
4	Luk adgangsstedet.

8.0 Leveringsvilkår

THV leveres steril og ikke-pyrogenisk emballeret i glutaraldehyd med stødpuder i en plastickrukke, hvor der er påsat en sikkerhedsforsegling. Hver krukke forsendes i en æske, der indeholder en temperaturindikator, som angiver, om THV'en har været udsat for ekstreme temperaturer under transporten. Æsken indkapsles derefter i Styrofoam inden forsendelsen.

Fremføringssystemet og tilbehøret leveres indpakket og steriliseret med ethylenoxid. Atrion QL2530 og QL38 anordningerne leveres i en termoformet oppakningsbakke og steriliseret med ethylenoxid.

8.1 Opbevaring

THV'en skal opbevares ved 10°C–25°C (50°F–77°F). Fremføringssystemet og tilbehøret bør opbevares på et køligt og tørt sted.

9.0 MR sikkerhed

MR **MR-sikker m/forbehold**

Ikke-kliniske test har vist, at en MR-scanning kan udføres på THV'en (implantatet) med betingelser. Den kan scannes sikkert under følgende forhold:

- Statisk magnetisk felt af 1,5 Tesla (T) eller 3,0 Tesla (T).
- Rumligt gradientfelt på 2500 gauss/cm eller mindre.
- Maks. gennemsnitlig helkrops specific absorption rate-værdi (WB-SAR) på 2,0 W/kg for 15 minutters scanning.
- Normal funktion, som defineret i IEC 60601-2-33, Ed. 2,0, på MR-systemet.

Ved en ikke-klinisk test og analyse konstateredes implantatet at udvikle en *in vivo* temperaturstigning på mindre end 1,3°C over baggrunden for en WB-SAR på 2,0 W/kg for 15 minutters MR-scanning i et 1,5 T cylindrisk GE Signa MR-system til hele kroppen. Den forventede *in vivo* stigning over baggrund var 1,5°C for en WB-SAR på 2,0 W/kg i et 3.0 T GE Signa HDxt 3T MR system. Disse beregninger overvurderer den sande *in vivo*-stigning, idet der ikke er taget hensyn til blodets kølevirkning.

Image-artefaktet går så vidt som 10 mm fra implantat for spin-ekko-imaging og 30 mm for gradient ekko-imaging, når der scannes i ikke-kliniske forsøg med et 3,0 T GE Signa HDx MR-system.

Implantatet er ikke blevet evalueret i andre MR-systemer end 1,5 T eller 3,0 T.

10.0 Patientinformation

Der følger en patientregistreringsformular med hver THV. Opgiv venligst alle de anmodede oplysninger efter implantation. Serienummeret findes på emballagen og på det identifikationsmærke, der sidder på THV'en. Returnér den originale formular til Edwards Lifesciences' adresse, som er anført på formularen, og giv det midlertidige identifikationskort til patienten inden udskrivning.

11.0 Udtagne THV og bortskafning af anordningen

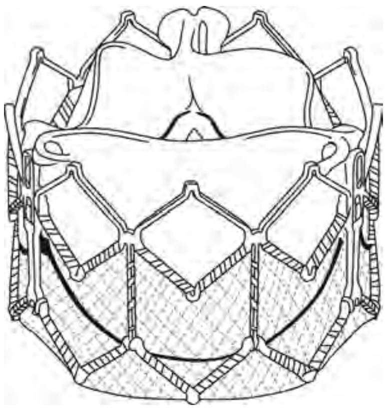
De eksplanterede THV'er bør anbringes i et passende histologisk fikseringsmiddel, såsom 10% formalin eller 2% glutaraldehyd og returneres til firmaet. Nedkøling er ikke nødvendig under disse omstændigheder. Kontakt Edwards Lifesciences for at få et eksplanterings-sæt.

Brugte anordninger kan håndteres og bortskaffes på samme måde som hospitalsaffald og biologiske farlige materialer. Der findes ingen særlige risici forbundet med bortskaffelse af disse anordninger.

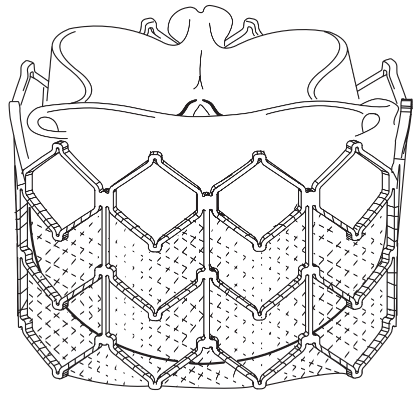
Disse produkter fremstilles og markedsføres under et eller flere af følgende amerikanske patenter: Amerikansk patentnr. 5,411,552; 5,931,969; 6,210,957; 6,214,054; 6,547,827; 6,561,970; 6,893,460; 6,908,481; 7,214,344; 7,510,575; 7,530,253; 7,585,321; 7,780,723; og RE40570 og tilsvarende udenlandske patenter. Der er yderligere anmeldte patenter.

12.0 Figures / Figurer

THV132



THV188



Valve Size Klaffstorlek Klapstørrelse	Height Höjd Højde
23 mm	14,3 mm
26 mm	17,2 mm

Valve Size Klaffstorlek Klapstørrelse	Height Höjd Højde
29 mm	19,1 mm

Figure 1. Edwards SAPIEN XT Transcatheter Heart Valve
Figur 1. Edwards SAPIEN XT kateterinförd hjärtklaff
Figur 1. Edwards SAPIEN XT transkateterhjerteklap

THV117

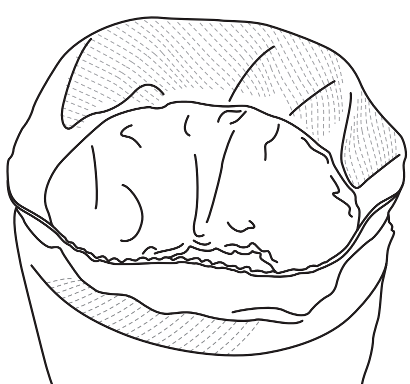


Figure 2. Qualcrimp Crimping Accessory
Figur 2. Qualcrimp krimptillbehör
Figur 2. Qualcrimp kompressionstilbehør

NF2THV04

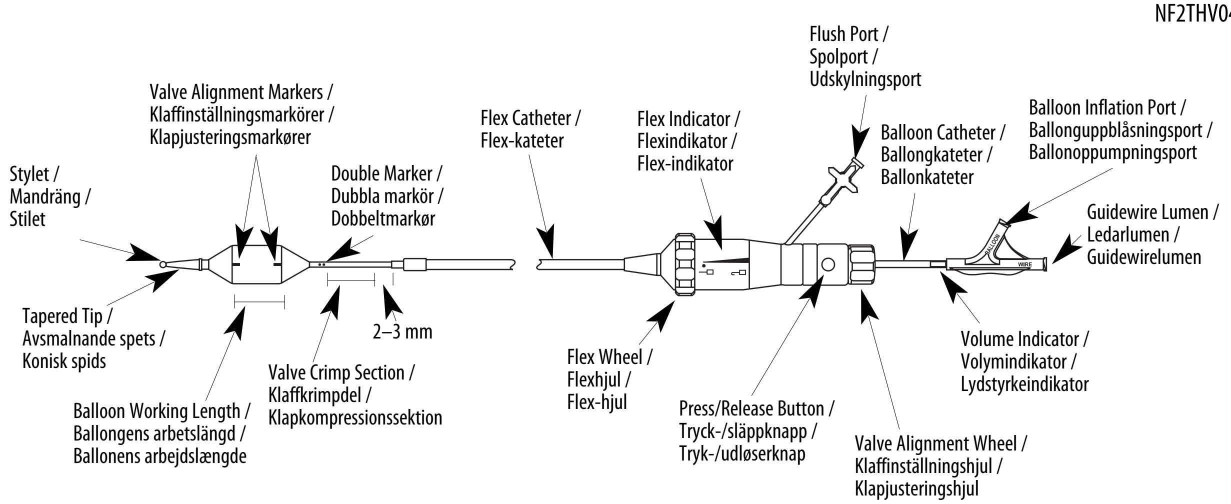


Figure 3a. NovaFlex+ Delivery System
Figur 3a. NovaFlex+ införingssystem
Figur 3a. NovaFlex+ fremføringssystem

NF2THV1

Figure 3b. Default Position
Figur 3b. Standardposition
Figur 3b. Default-position

NF2THV2

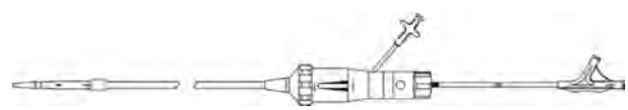
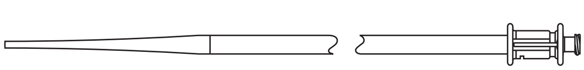


Figure 3c. Valve Alignment Position
Figur 3c. Klaffinställningsposition
Figur 3c. Klapjusteringsposition

THV113



Model Modell	Dilators Dilatatorer
9100DKS	16F, 18F, 20F, 22F

Figure 4. RetroFlex Dilator Kit
Figur 4. RetroFlex dilatatorsats
Figur 4. RetroFlex-dilatatorsæt

THV214

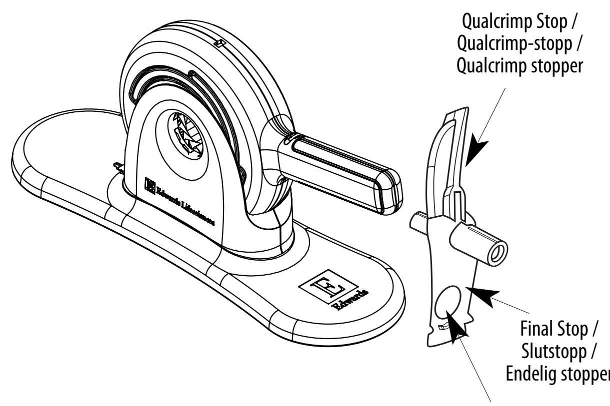


Figure 5. Crimper and 2-piece Crimp Stopper
Figur 5. Krimpverktyg och 2-delad krimpstopper
Figur 5. Kompressionsanordning og todelt kompressionsstopper

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Symbol Legend • Förklaring av symboler • Symbolforklaring

	English	Svenska	Dansk
REF	Catalogue Number	Katalognummer	Katalognummer
REF	Catalogue Number	Katalognummer	Katalognummer
#	Quantity	Antal	Antal
I	Minimum Introducer Size	Minsta introducerstorlek	Min. størrelse på indførings-anordning
cm	Usable Length	Användbar längd	Brugslængde
	Single Use	Endast för engångsbruk	Engangsbrug
	Attention, See Instructions for Use	OBS! Se bruksanvisning	Bemærk, se brugsanvisningen
	Do not use if package is opened or damaged	Använd inte om förpackningen har öppnats eller skadats.	Må ikke anvendes, hvis emballagen er åbnet eller beskadiget.
	Do not use if package is damaged	Använd inte om förpackningen har skadats	Må ikke anvendes, hvis pakken er beskadiget
Rx only	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.		
	Exterior Diameter	Yttre diameter	Udvendig diameter
	Inner Diameter	Innerdiameter	Indvendig diameter
	Store in a cool, dry place.	Förvara produkten svalt och torrt.	Skal opbevares køligt og tørt.
STERILE	Sterile	Steril	Steril
STERILE EO	Sterilized Using Ethylene Oxide	Steriliserad med etylenoxid	Steriliseret ved brug af ethylenoxid
STERILE R	Sterilized Using Irradiation	Steriliserad med strålning	Steriliseret ved bestråling
STERILE	Sterile Using Steam or Dry Heat	Steriliserad med ånga eller varmluft	Steril ved brug af damp eller tør varme
LOT	Lot Number	Lotnummer	Partinummer
	Use By	Använd före	Udløbsdato
SN	Serial Number	Serienummer	Serienummer
	Manufacturer	Tillverkare	Producent
EC REP	Authorised Representative In The European Community	Auktoriserad representant inom Europeiska gemenskapen	Autoriseret repræsentant i EU
GW	Recommended Guidewire Size	Rekommenderad ledarstorlek	Anbefalet ledetrådsstørrelse
SZ	Size	Storlek	Størrelse
Contents	Contents	Innehåll	Indhold

	English	Svenska	Dansk
GWC	Guidewire Compatibility	Ledar-kompatibilitet	Ledetråds-kompatibilitet
NP	Nominal Pressure	Nominellt tryck	Nominelt tryk
RBP	Rated Burst Pressure	Angivet sprängtryck	Normeret sprængningstryk
STRAIGHT	Straight	Rak	Lige
DEFLECTED	Deflected	Böjd	Bøjelig
MR	MR Conditional	MR-säker	MR-sikker m/forbehold
	Recommended Guidewire Length	Rekommenderad ledarlängd	Anbefalet ledetrådslængde
Sheath	Minimum Sheath Size	Minsta hylsstorlek	Min. hylsterstørrelse
Catheter	Catheter Shaft Size	Kateter-skaftstorlek	Kateter-skaftstørrelse
	Balloon Diameter	Ballongdiameter	Ballondiameter
	Balloon Working Length	Ballongens arbetslängd	Ballonens arbejdslængde
10 °C 25 °C	Temperature Limitation	Temperatur-begränsningar	Temperatur-begrænsning
23 mm	For use with size 23mm Edwards transcatheter heart valve	För användning med Edwards kateterinförda hjärtklaff, 23 mm	Til brug med Edwards transkateterhjerteklap størrelse 23 mm
26 mm	For use with size 26mm Edwards transcatheter heart valve	För användning med Edwards kateterinförda hjärtklaff, 26 mm	Til brug med Edwards transkateterhjerteklap størrelse 26 mm
23 mm 26 mm	For use with size 23mm or size 26mm Edwards transcatheter heart valve	För användning med Edwards kateterinförda hjärtklaff, 23 mm eller 26 mm	Til brug med Edwards transkateterhjerteklap størrelse 23 mm eller 26 mm
29 mm	For use with size 29mm Edwards transcatheter heart valve	För användning med Edwards kateterinförda hjärtklaff, 29 mm	Til brug med Edwards transkateterhjerteklap størrelse 29 mm
PHT	Contains phthalates	Innehåller ftalater	Indeholder phtalater
NON STERILE	Non-sterile	Osteril	Ikke-sterilt
	Nonpyrogenic	Icke-pyrogen	Nonpyrogent

Note: Not all symbols may be included in the labeling of this product.
Obs! Alla symboler inkluderas eventuellt inte i produktmärkningen.
Bemærk: Alle symbolerne er muligvis ikke inkluderet på produktmærkaterne.

Edwards

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CE 0344

11/11
149809002 Rev. B

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APPENDIX G

A Randomized Evaluation of the SAPIEN XT Transcatheter Valve System in Patients with Aortic Stenosis Who Are Not Candidates for Surgery: PARTNER II, Inoperable Cohort

Martin B. Leon, MD
on behalf of The PARTNER Trial Investigators

ACC 2013 | San Francisco | March 10, 2013

THE PARTNER II TRIAL

Disclosure Statement of Financial Interest

Martin B. Leon, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Grant/Research Support	Abbott, Boston Scientific, Edwards Lifesciences, Medtronic
Consulting Fees/Honoraria	None
Major Stock Shareholder/Equity	Sadra, Claret, Valve Medical, Apica

THE PARTNER II TRIAL